

ORGAN/TISSUE	CONTROL (SALINE)	SOLVENT (DMSO/PG)	LSSBio-294 2 mg/kg	LSSBio-294 10 mg/kg
BRAIN	NS*	NS	NS	NS
SKELETAL MUSCLE	NS	NS	NS	NS
HEART	NS	NS	NS	NS
THYMUS	NS	NS	NS	NS
LUNG	NS	NS	NS	NS
LIVER	NS**	NS	NS	NS
SPLEEN	NS	NS	NS	NS
DUODENUM	NS	NS	NS	NS
PANCREAS	NS	NS	NS	NS
KIDNEY	NS	NS	NS	NS
SUPRARENAL	NS	NS	NS	NS
URINARY BLADDER	NS	NS	NS	NS

* NS INDICATES NO SIGNIFICANT CHANGE WHEN COMPARED TO A CONTROL UNINJECTED ANIMAL.

** ONE ANIMAL OF THE CONTROL (SALINE) GROUP SHOWED AN INFLAMMATORY PROCESS (MONONUCLEAR INFILTRATION) IN THE LIVER.

FIG. 1A

DAY	SALINE						SOLVENT						LASSBio-294						LASSBio-294					
	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
1	18	16.4	19.4	17.4	17.7	18.4	18.6	19.8	17.2	17.7	16.2	18.9	M	M	M	15.8	16.5	15.7	15.6	15	15	16.3	15.7	15
2	18.6	16.4	18.3	17.3	17.6	18.8	17.6	18.8	16	17.8	14.7	18.2	18.8	17.2	16	D	15.2	14.6	15.8	14.7	14.9	16.7	15.7	15.7
3	18.5	16.3	18.4	17.6	18.6	19.4	18.2	18.3	16.6	17.3	14.2	19	18.3	18.2	16.3		15	14.4	16.5	15	15	17.9	16.7	17
4	19.3	16.6	18.6	17.7	18.3	20.1	18.3	17.4	16.6	16.9	13.6	18.4	19	16.8	16.6		15	14.6	16.6	14.8	15.4	18	17.4	16.5
5	19.9	16.8	18.2	17.9	19	20.5	18.8	16.6	17.5	16.7	D	18.7	20	17	17.2		15.5	14.7	16.9	15.7	15.8	18.4	18	17.1
6	21	17.8	18	18.5	20	22.5	20.4	17.2	19	16		20.2	21.8	19	19.1		18.1	15.4	17.5	16.6	15.8	19.6	19.2	17.9
7	21.5	18	18	18.8	20	23	21	18	20	16.5		20.5	22	20	19.5		18.5	16	18	17	16	20	20	18.1
8	20	17	18	18	19.7	22.5	19	17.7	18.7	14.6		20	22	17.9	18		16.9	14.5	17	15.5	14.8	18.7	20	17
9	19.2	20	18.4	18.4	20	22.9	20.4	18.8	18.5	D		21.3	21.2	15.8	17.6		17	14.4	16.9	15.5	15	18.2	18	16.6
10	20.8	19	18.5	19	19.5	22	21	18	18.5			20.5	21	16	17.5		16.5	15	19.5	18	15.3	18.5	19.1	17
11	21.5	19	19	18	19	22.5	21.9	19	18.7			21	19.8	16.5	18		17	16	20	19	17	19	19.5	18
12	20.5	17.5	17.5	18.5	20.5	23.3	21.3	19.7	20.1			22.4	24.1	19.7	18.9		17.5	15.3	17.7	15.9	15.5	20.2	20.1	18.5
13	20.4	17.2	17.2	18.2	20.9	22.9	22.1	19.7	21.2			23.2	24.5	21.3	18.6		17.7	15.6	17.3	15.9	15	23.3	19.7	18.6
14	20.9	17.8	17.8	18.2	21	23.2	22.4	19	21			23.4	25.5	21.5	19		18.8	16.8	17.8	16.4	15.1	19.1	20.6	18.7
15	20.6	17.4	17.4	18.2	20.8	23.3	22.3	18.8	21.5			23.1	26.3	21.9	18.9		19.4	16.2	18.7	16.5	15	19.9	20	18.6

FIG. 1B

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	MOUSE #	HEMATO CRIT (%)	MEAN	S.D.	Lecx10 ³ /m	m3	MEAN	S.D.	HEM.	/mm3	MEAN	S.D.
SALINE	1		44.5	0.71			4.93	3.15			9.77	3.41
	2	44			143	7.15			981	7.36		
	3	41			275	13.75			681	10.2		
	4	48			47	2.35			453	13.6		
	5	47			20	1			417	12.51		
	6	45			54	2.7			406	12.18		
SOLVENT	1	43	44.0	1.14	54	2.7	3.76	1.43	333	5.99	10.33	2.92
	2											
	3	43			117	5.85			376	11.28		
	4											
	5	46			69	3.45			406	12.18		
	6	44			61	3.05			396	11.88		
LASSBio-294 2 mg/kg	1	47	46.2	1.30	89	4.45	3.76	1.04	418	12.54	12.38	0.83
	2	44			67	3.35			399	11.97		
	3	47			44	2.2			398	11.94		
	4											
	5	46			79	3.95			459	13.77		
	6	47			97	4.85			390	11.7		
LASSBio-294 10 mg/kg	1	49	48.5	0.71	40	2	2.80	1.13	385	11.55	10.50	1.48
	2	48			56	2.8			200	6		
	3	45			164	8.2			350	10.5		
	4	48			64	3.2			305	9.15		
	5	47			98	4.9			535	16.05		
	6	48			72	3.6			315	9.45		

FIG. 1C

	GLUCOSE mg/dl	UREA mg/dl	CREATINE mg/dl	TOTAL PROTEIN g/dl	ALBUMIN g/dl	GLOBULIN s g/dl	RATIO A/G	TGO U/l	TGP U/l
SALINE	182	57	0.4	6.1	3.8	2.3	1.6	148	80
	30	41	0.5	6.0	3.6	2.4	1.5	194	68
	45	51	0.5	5.6	-	-	-	233	62
	29	35	0.2	5.5	-	-	-	130	-
	170	56	0.5	5.3	3.6	1.7	2.1	164	65
SOLVENT	155	58	0.3	5.0	3.3	1.7	1.9	117	79
	105	61	0.3	4.8	2.8	2.0	1.4	152	69
	122	53	0.6	4.9	3.3	1.6	2.1	136	54
	124	55	0.3	5.3	3.4	1.9	1.7	154	63
LASSBio-294 2 mg/kg	97	55	0.5	4.8	3.1	1.7	1.8	106	56
	131	34	0.4	4.9	3.2	1.7	1.8	124	45
	175	77	0.2	6.0	-	-	-	101	-
	166	63	0.4	5.6	3.7	1.9	1.9	211	100
	93	65	0.4	6.0	-	-	-	198	84
LASSBio-294 10 mg/kg	179	45	0.4	-	-	-	-	259	92
	70	55	0.3	4.9	3.8	1.1	3.4	148	74
	86	91	0.6	-	-	-	-	137	50
	132	67	0.6	6.1	-	-	-	284	127
	134	72	0.5	7.7	-	-	-	100	64
	120	44	0.3	5.5	3.8	1.7	2.2	156	111

FIG. 1D

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DMSO	T _p (ms)	T _{0.5} (ms)	T _{0.8} (ms)
1	36	38	60
2	31	33	52
3	41	34	53
AVERAGE	36	35	55
SE	2.89	1.53	2.52
#294 (25uM)	T _p (ms)	T _{0.5} (ms)	T _{0.8} (ms)
1	42	38	58
2	41	30	48
3	41	31	49
AVERAGE	41	33	52
SE	0.33	2.52	3.18
AVERAGE (#294/DMSO)	1.14	0.94	0.95

FIG. 1E

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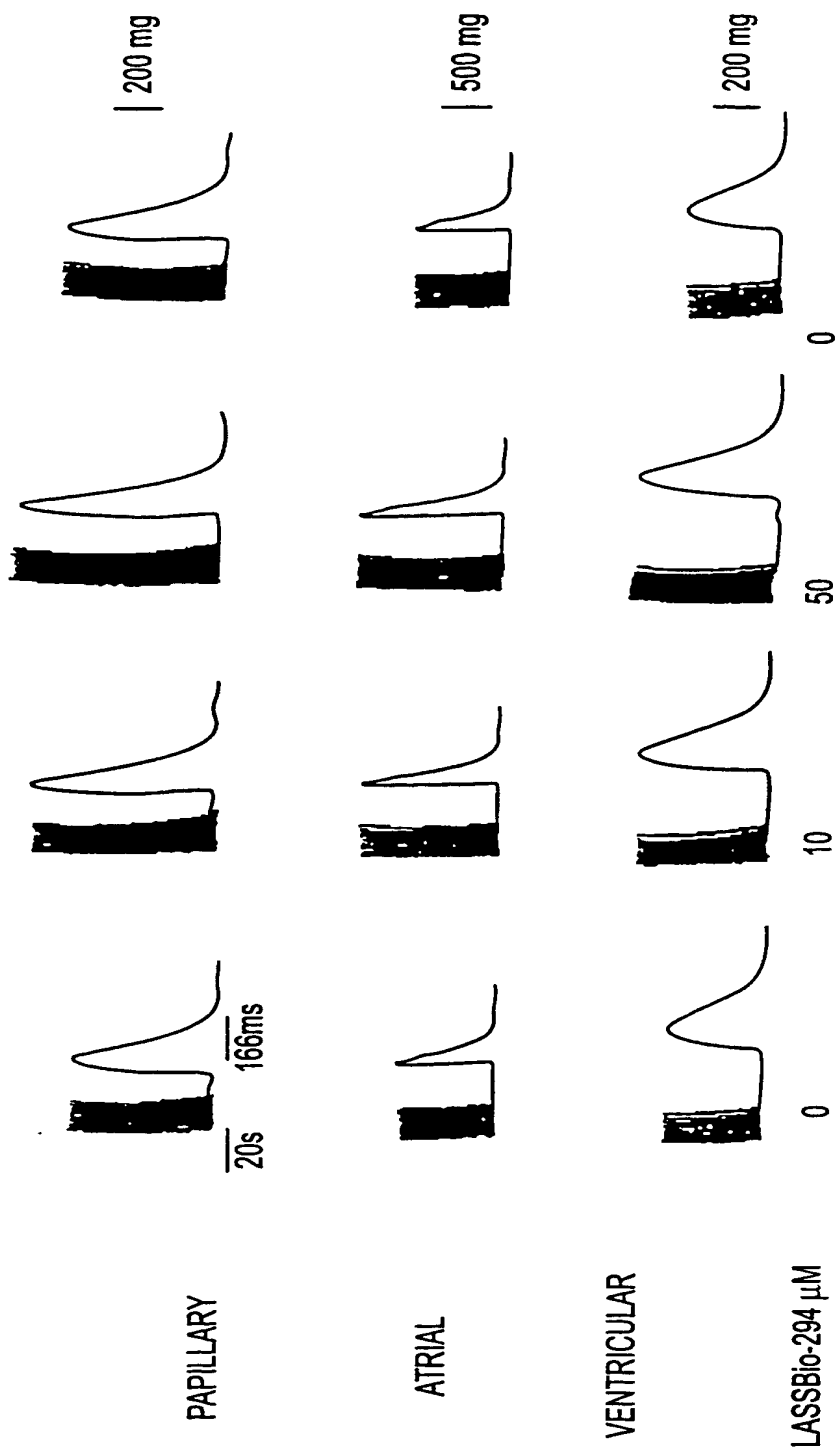


FIG. 2

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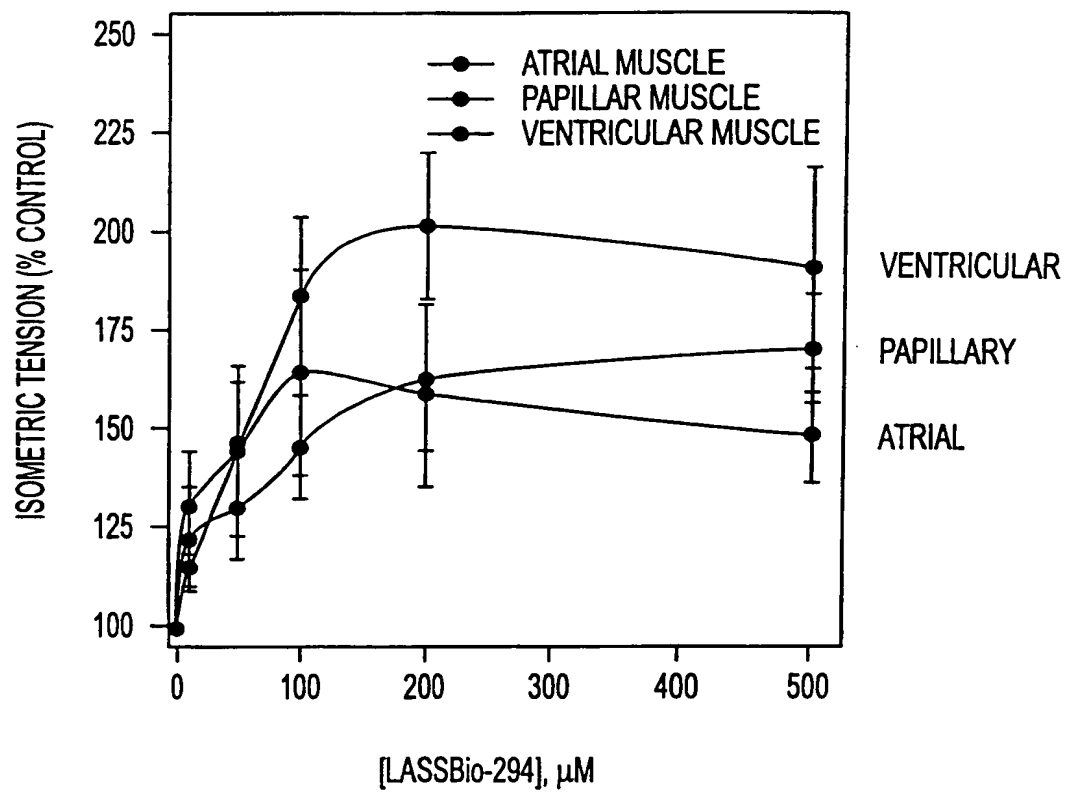


FIG. 3

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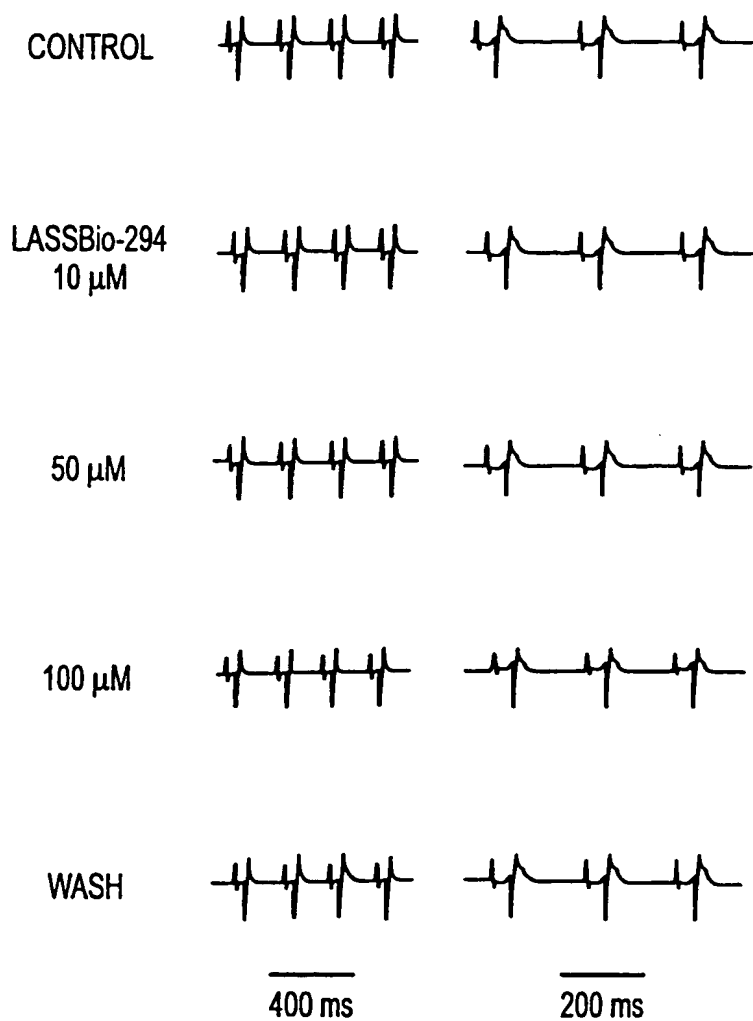


FIG. 4

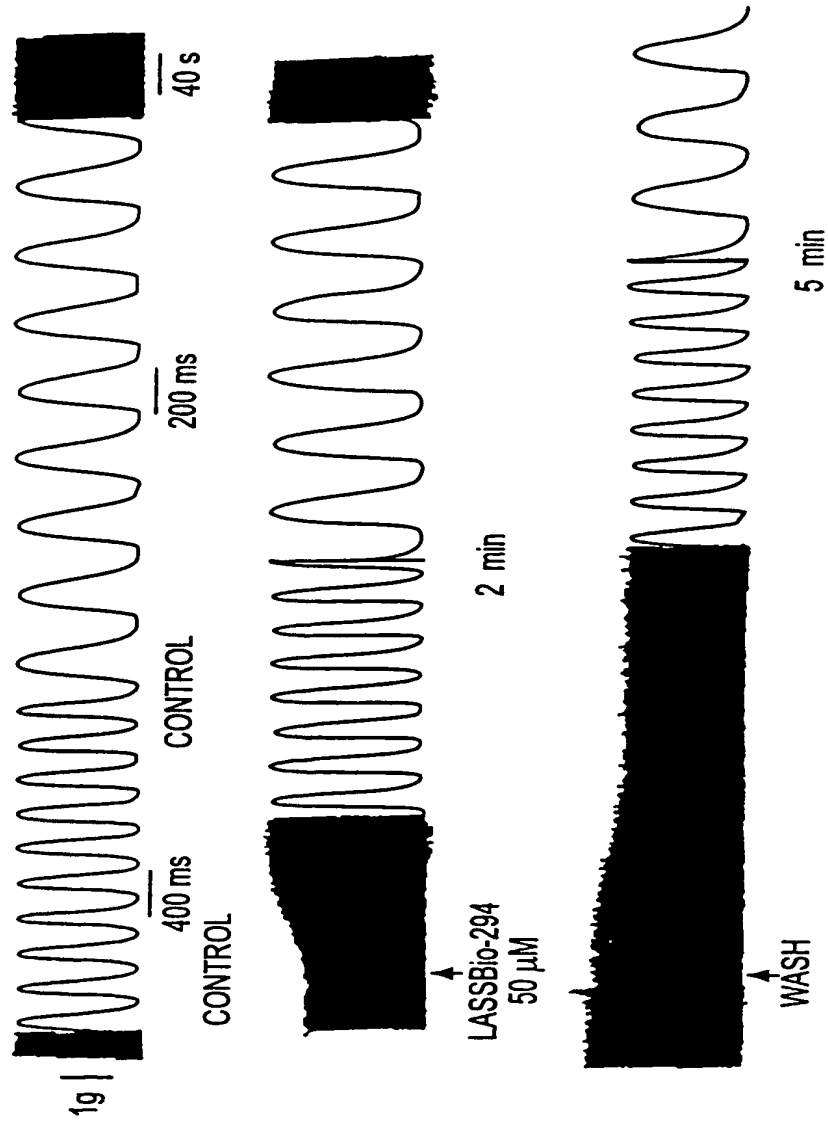


FIG. 5

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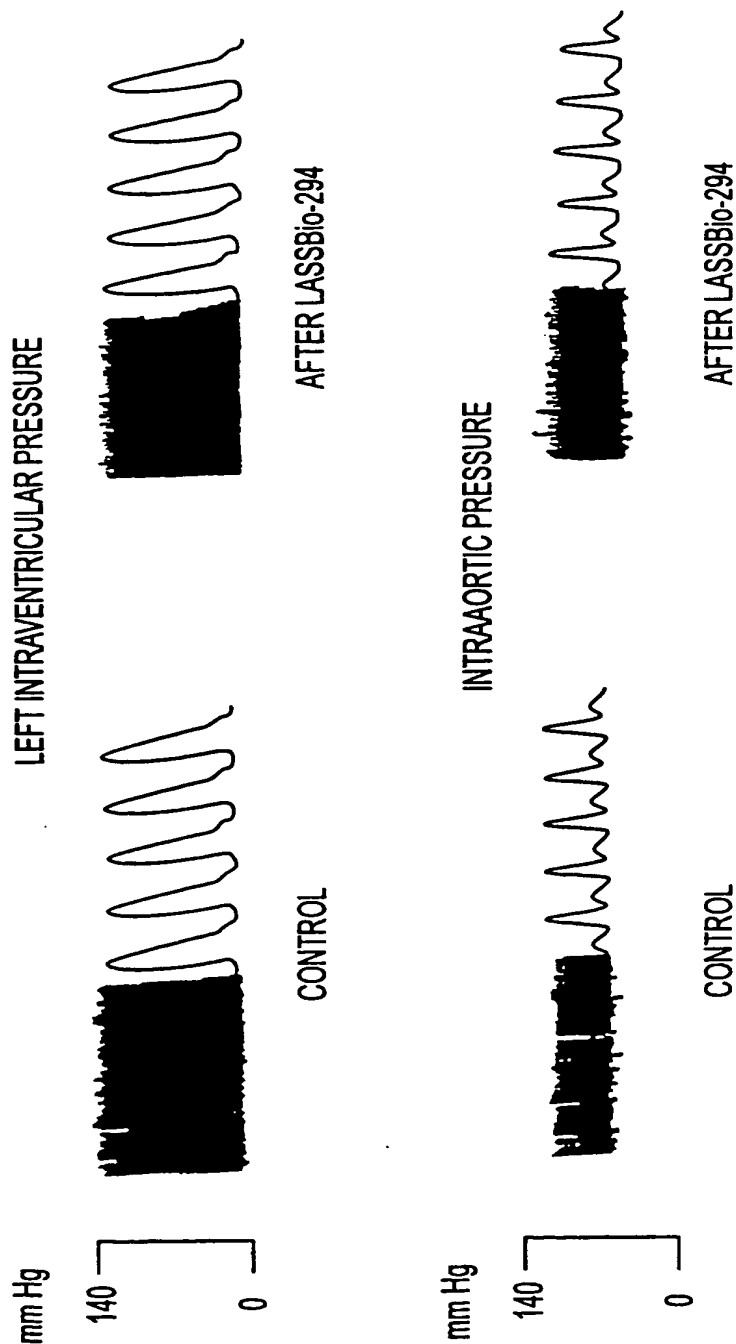


FIG. 6

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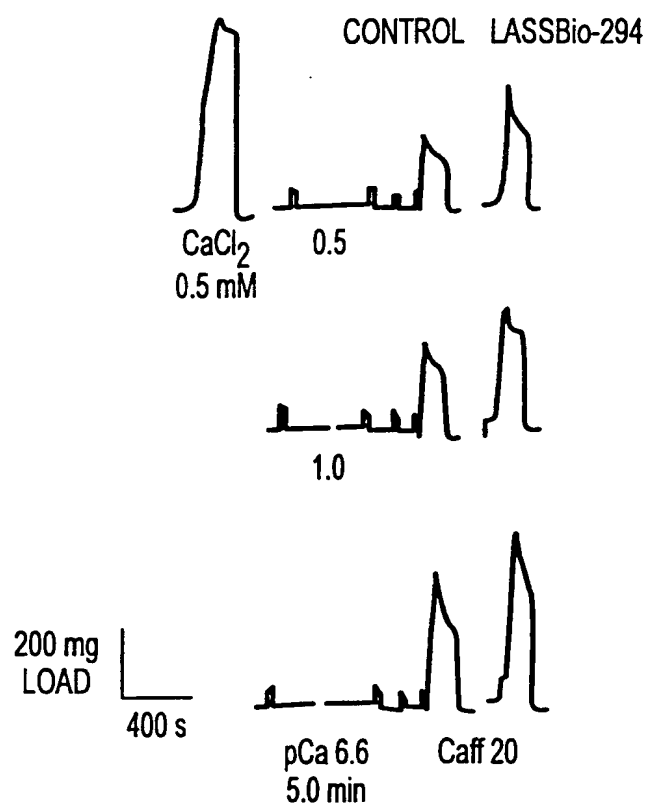


FIG. 7

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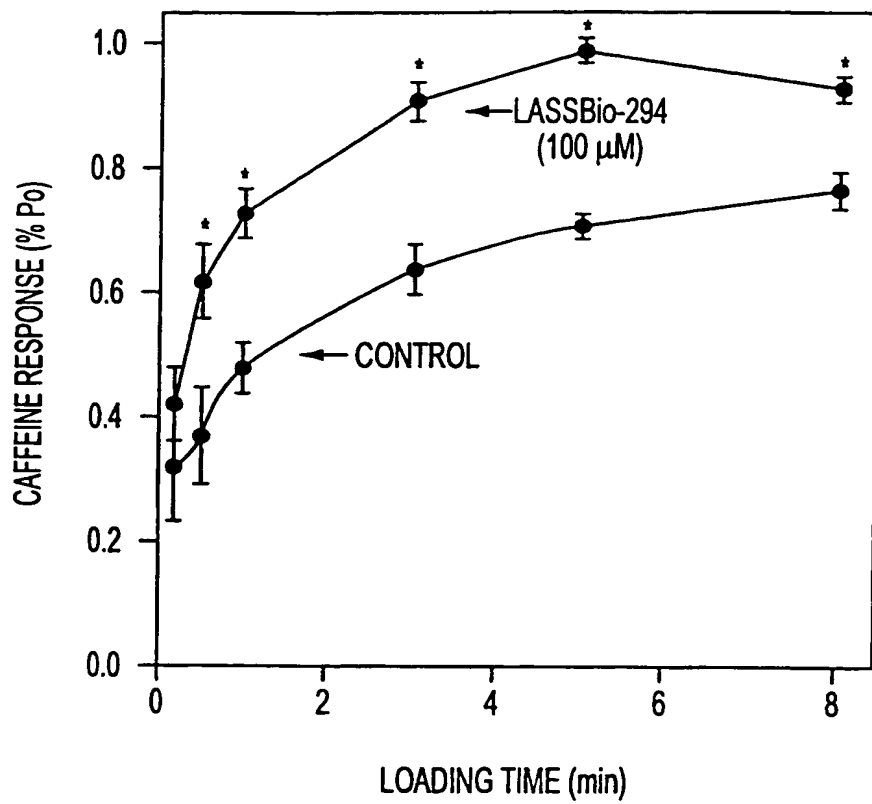


FIG. 8

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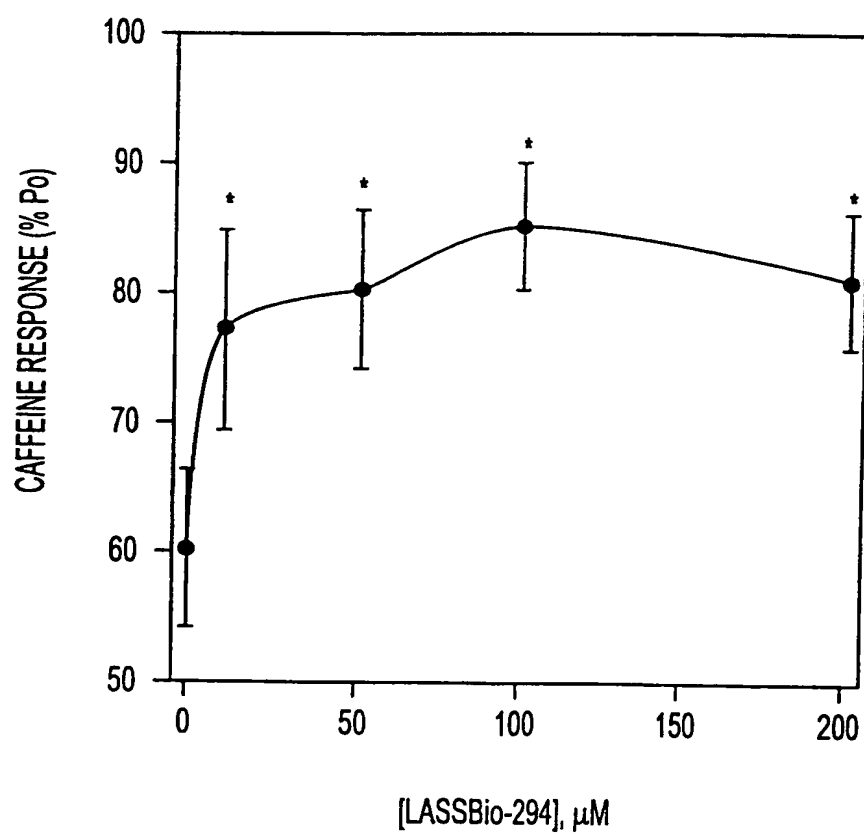


FIG. 9

INCREASE IN CONTRACTILE TENSION INDUCED BY CAFFEINE IN HEART VENTRICULAR FIBERS WITH SARCOLEMMA MEMBRANE REMOVED AFTER THE SARCOPLASMIC RETICULUM HAS BEEN LOADED WITH

LASSBio-294

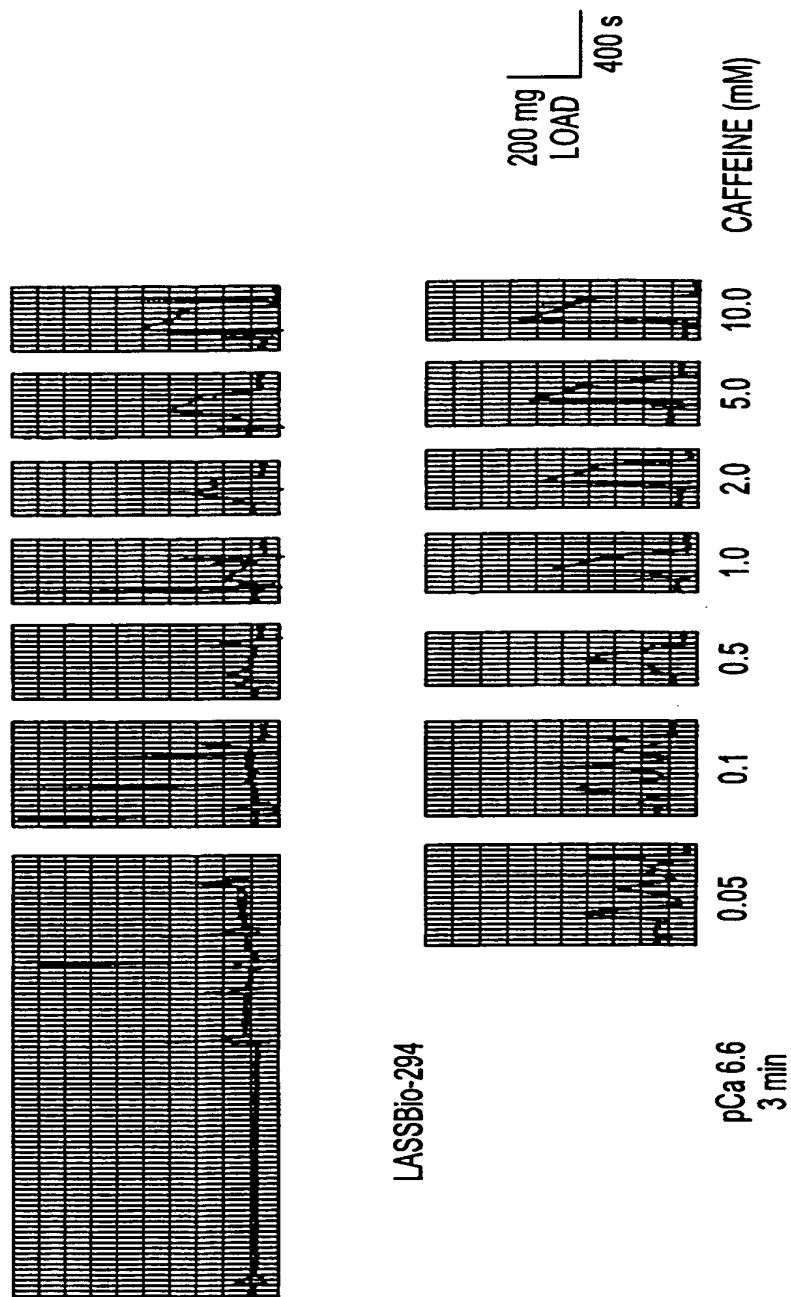


FIG. 10

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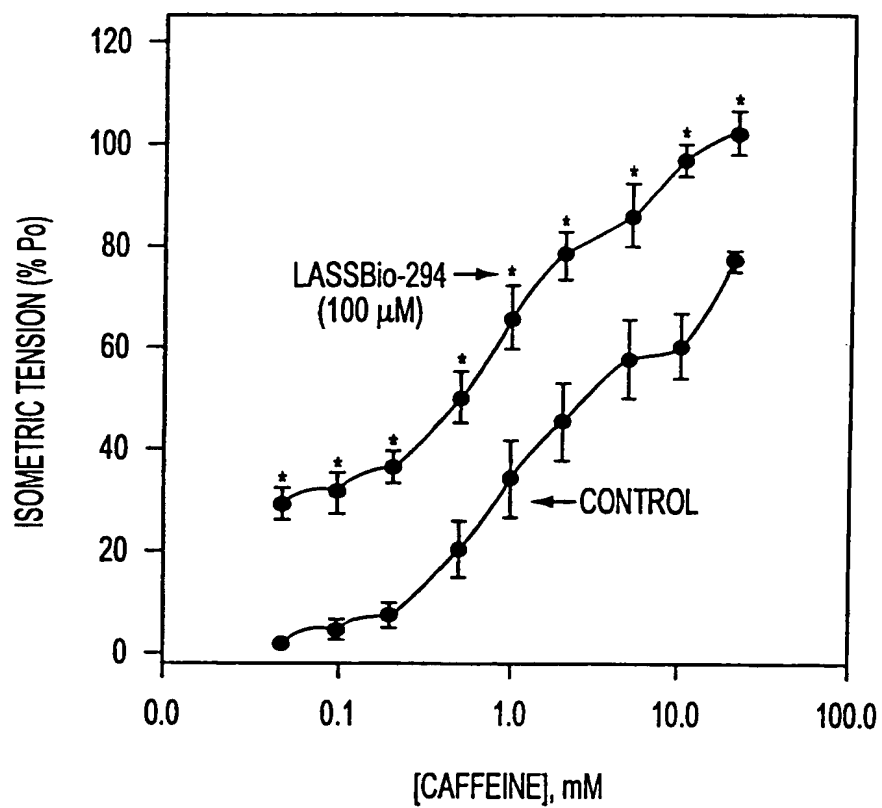


FIG. 11

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LASSBio-294 HAS NO EFFECT ON THE SENSITIVITY OF MYOFIBRILS TO Ca^{2+} IN CARDIAC FIBERS WITH SARCOLEMMA REMOVED AND WITH THE SARCOPLASMIC RETICULAR MEMBRANE DISRUPTED

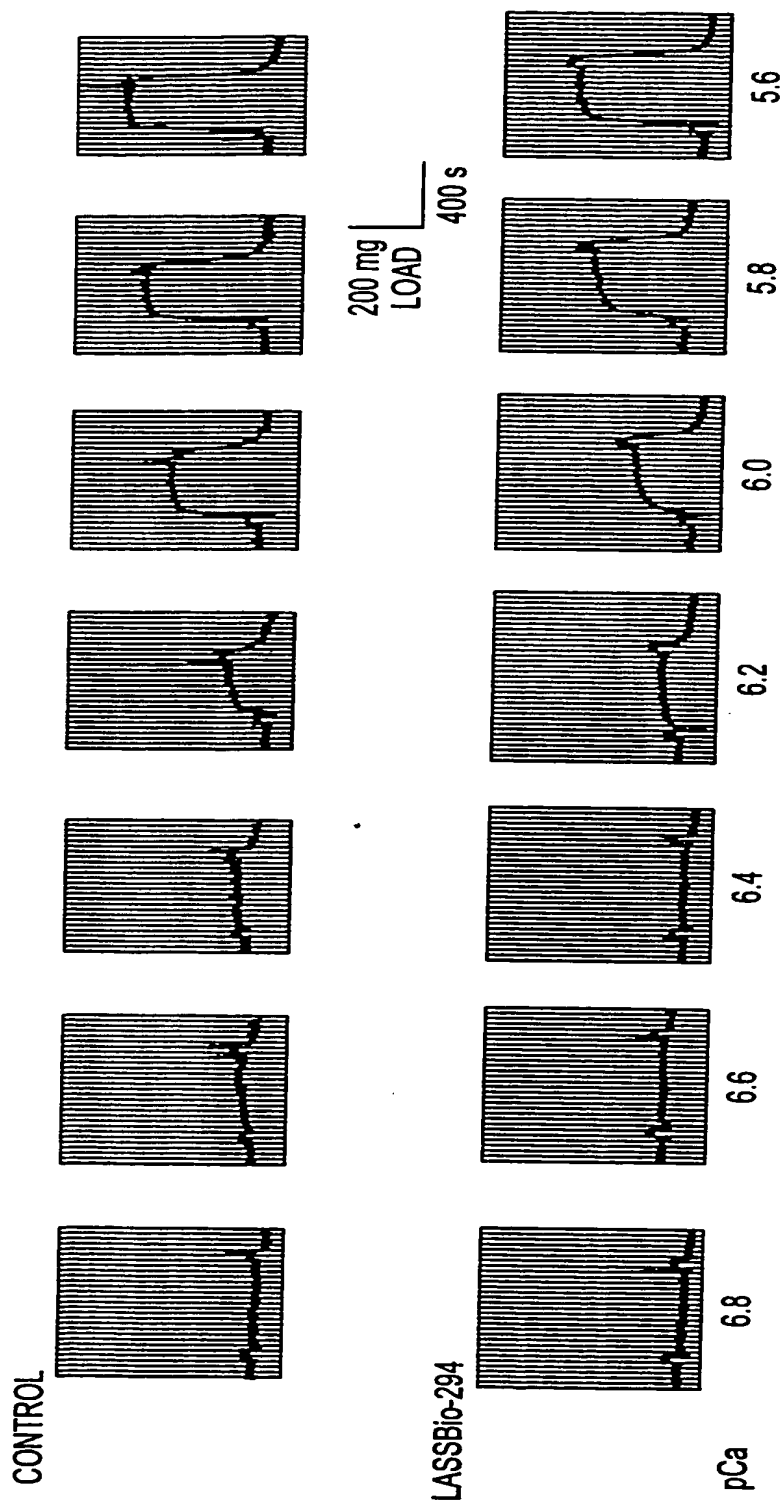


FIG. 12

LASSBio-294 HAS NO EFFECT ON THE ISOMETRIC TENSION INDUCED BY
VARIOUS CONCENTRATIONS OF Ca^{2+} IN CARDIAC FIBERS WITH
SARCOLEMMMA REMOVED AND SR MEMBRANES DISRUPTED

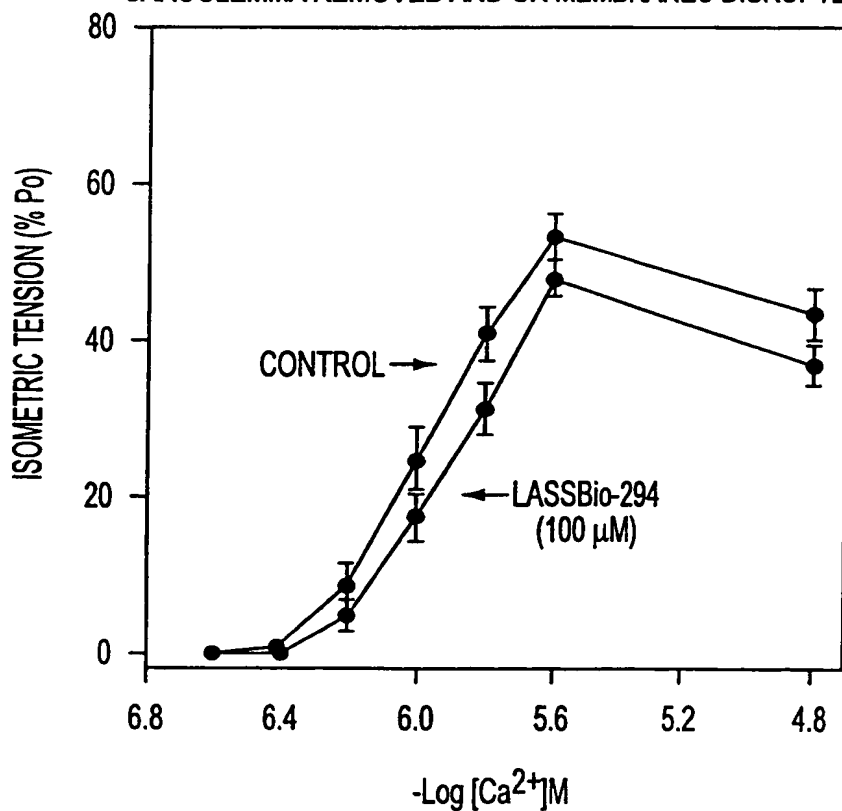
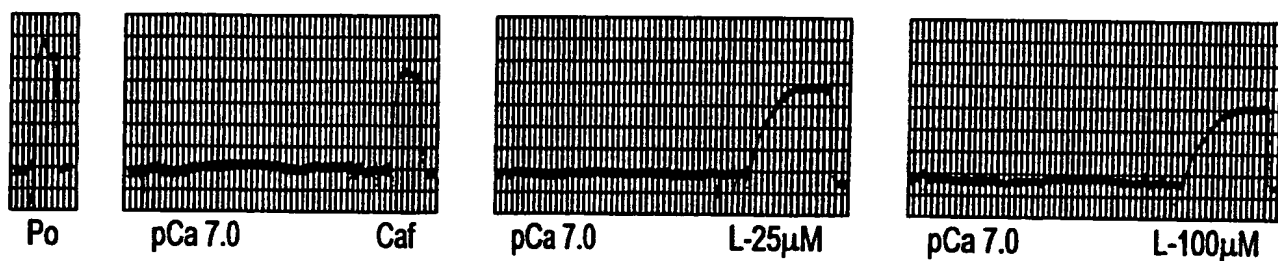


FIG. 13

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LASSBio-294-INDUCED RELEASE OF Ca^{2+} FROM THE SARCOPLASMIC RETICULUM OF ISOLATED HUMAN SKELETAL MUSCLE FIBERS WITH SARCOLEMMA REMOVED



200 mg
LOAD
400 s

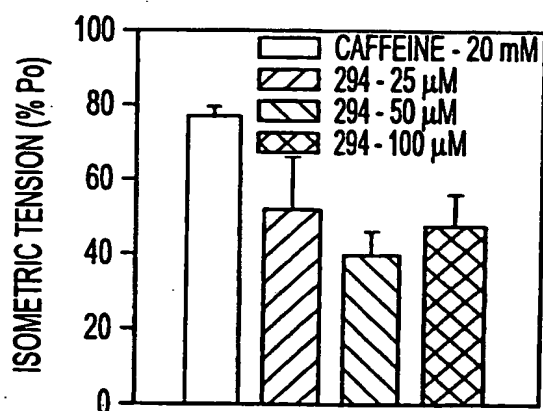


FIG. 14

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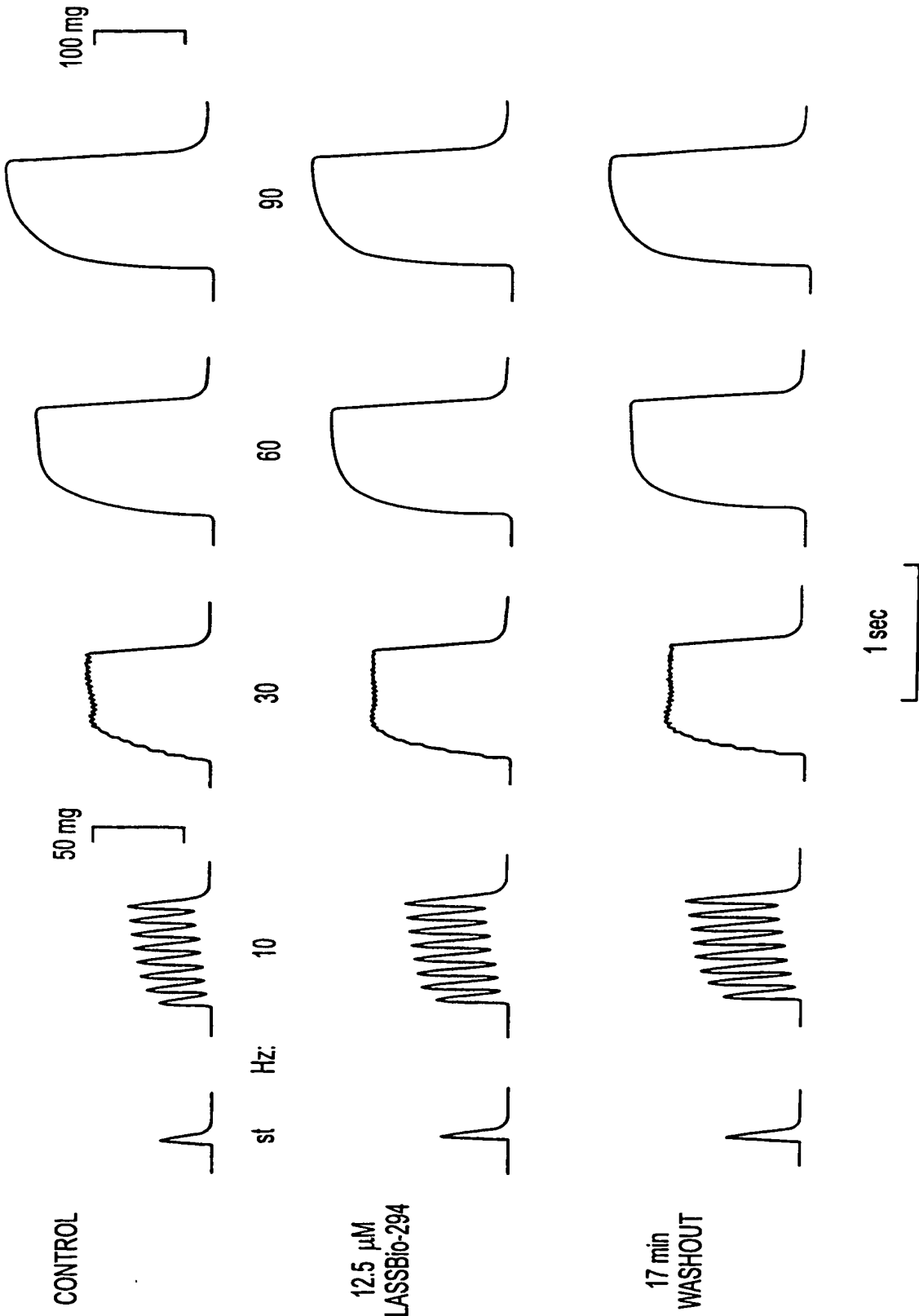


FIG. 15

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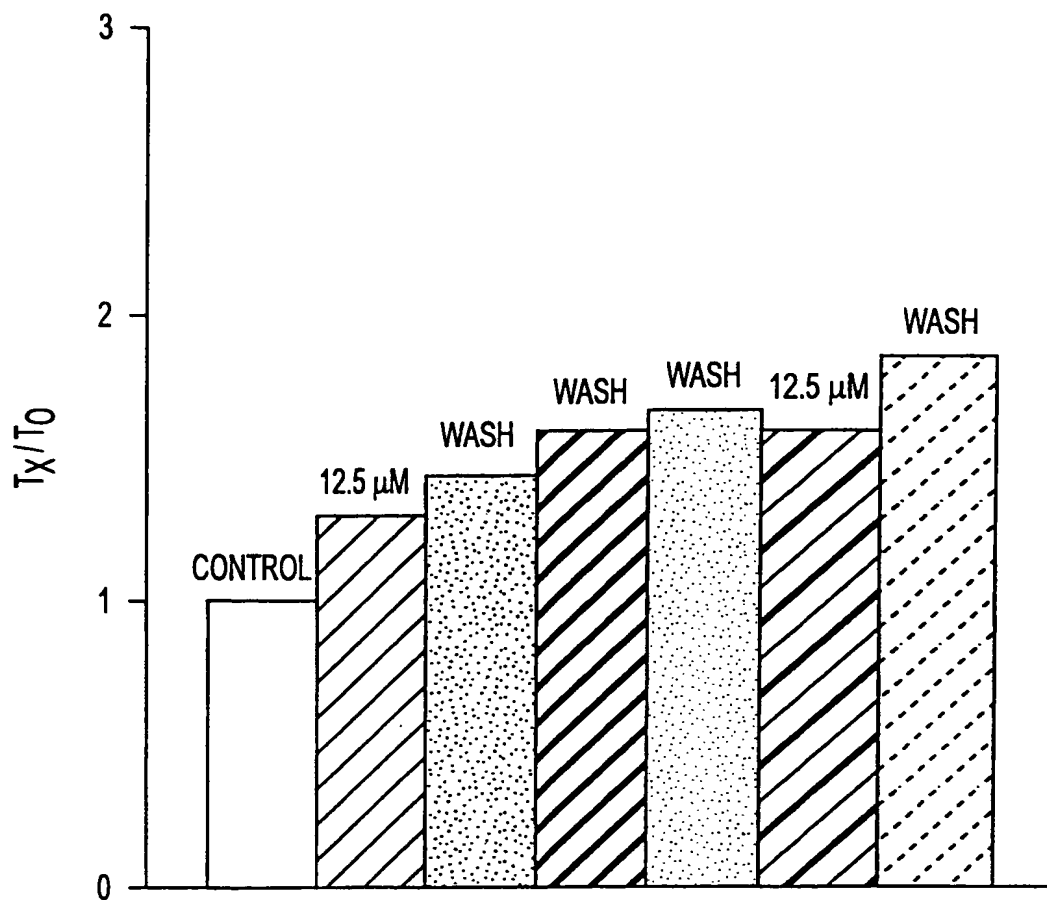
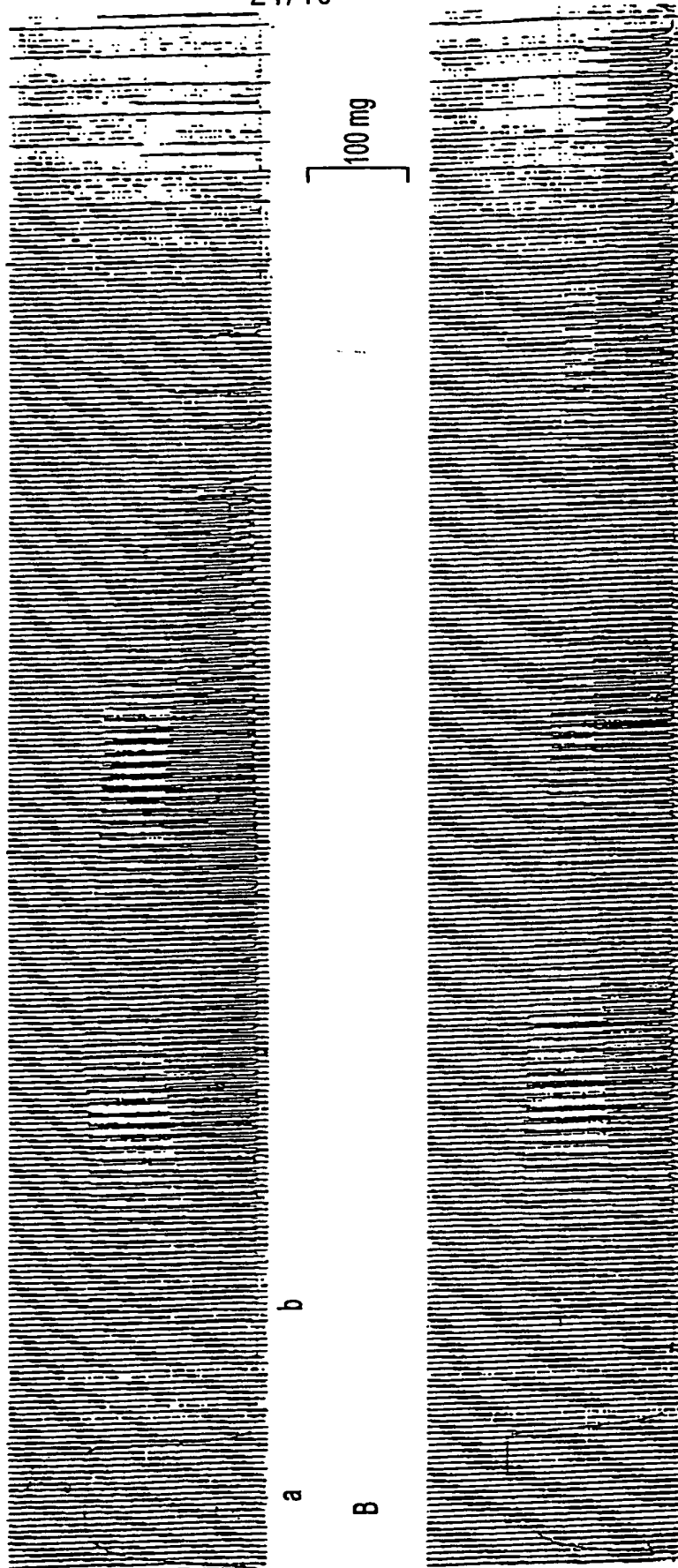


FIG. 16

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1 sec

1 min

a b

FIG. 17

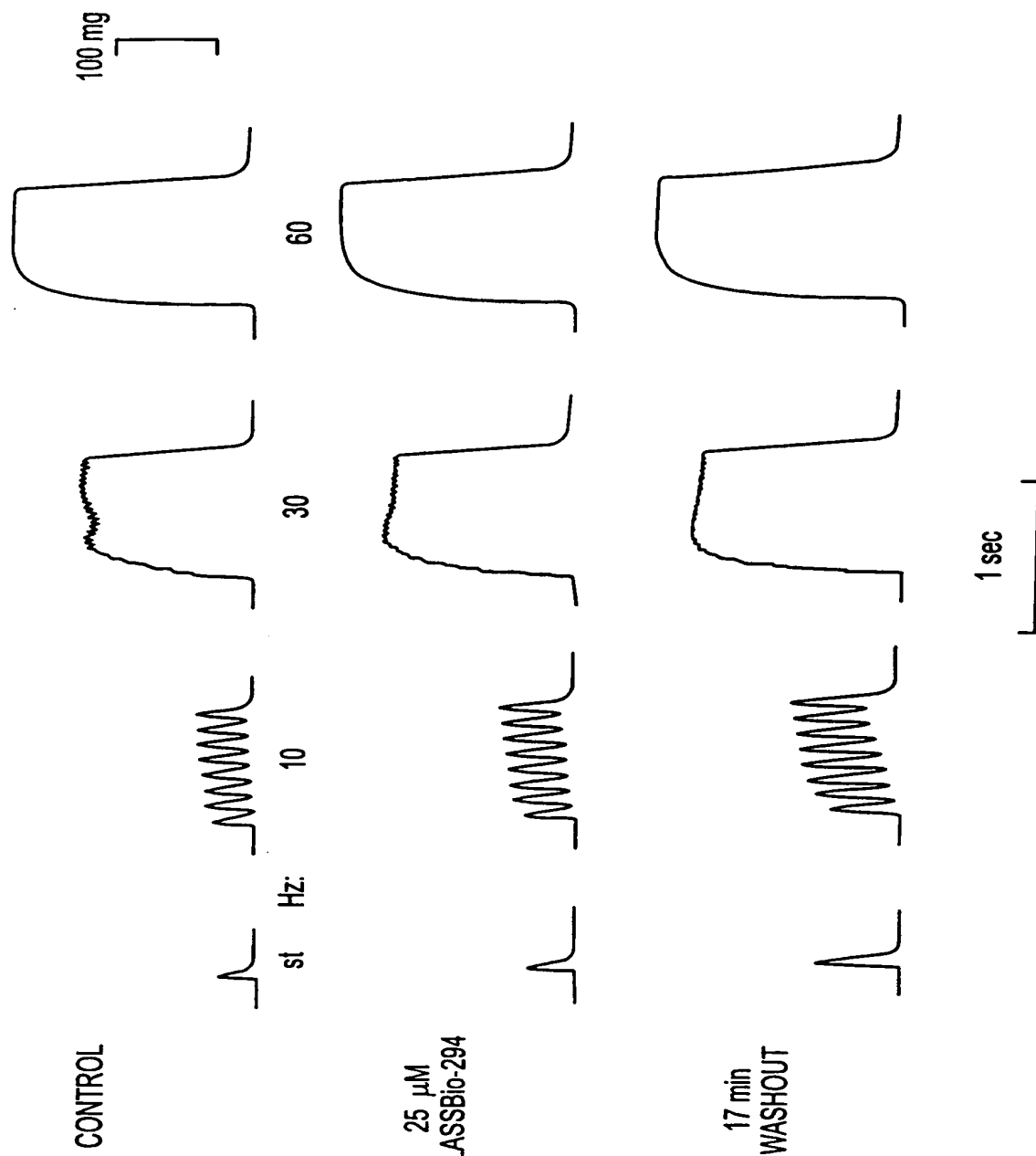


FIG. 18

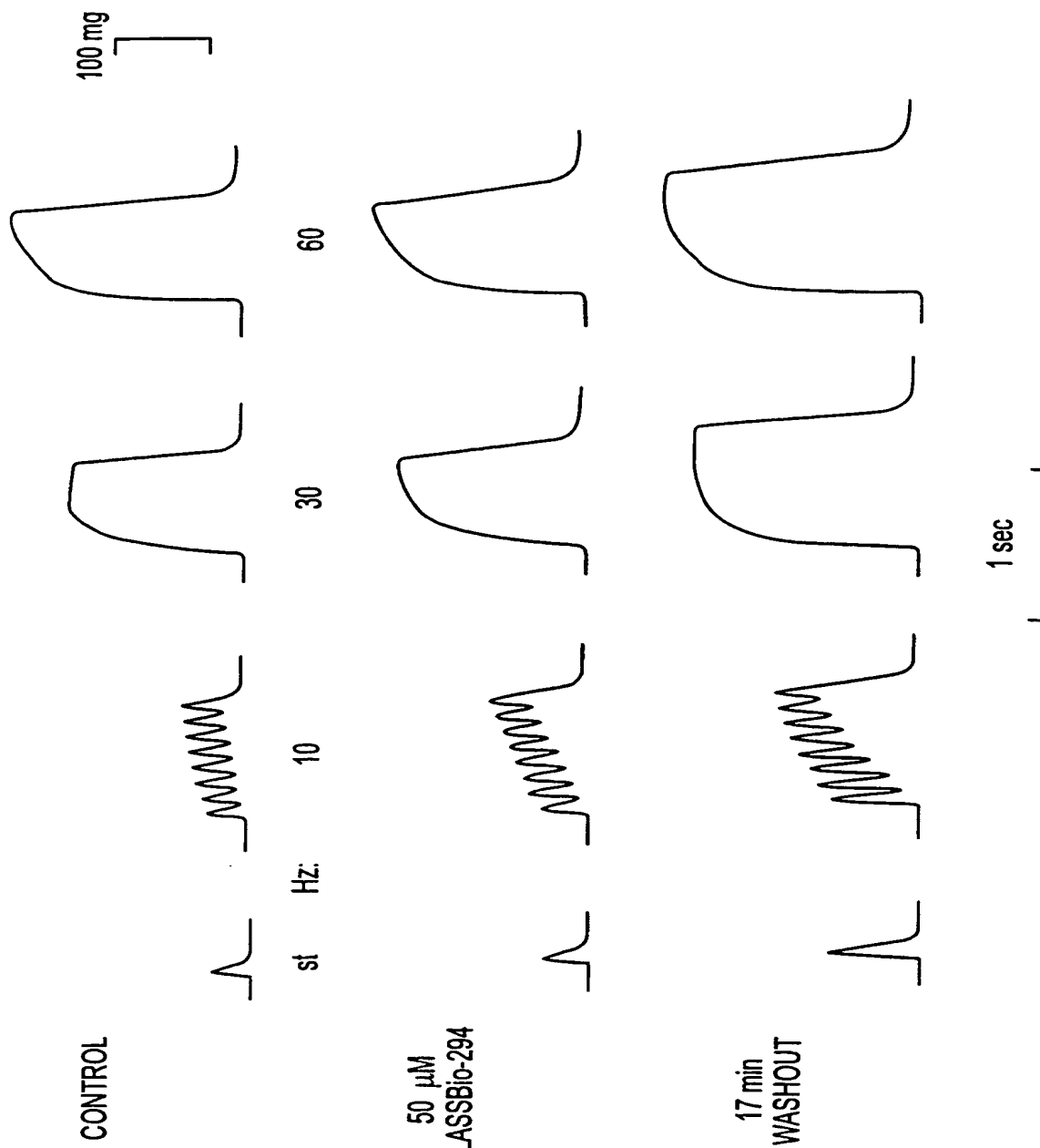


FIG. 19

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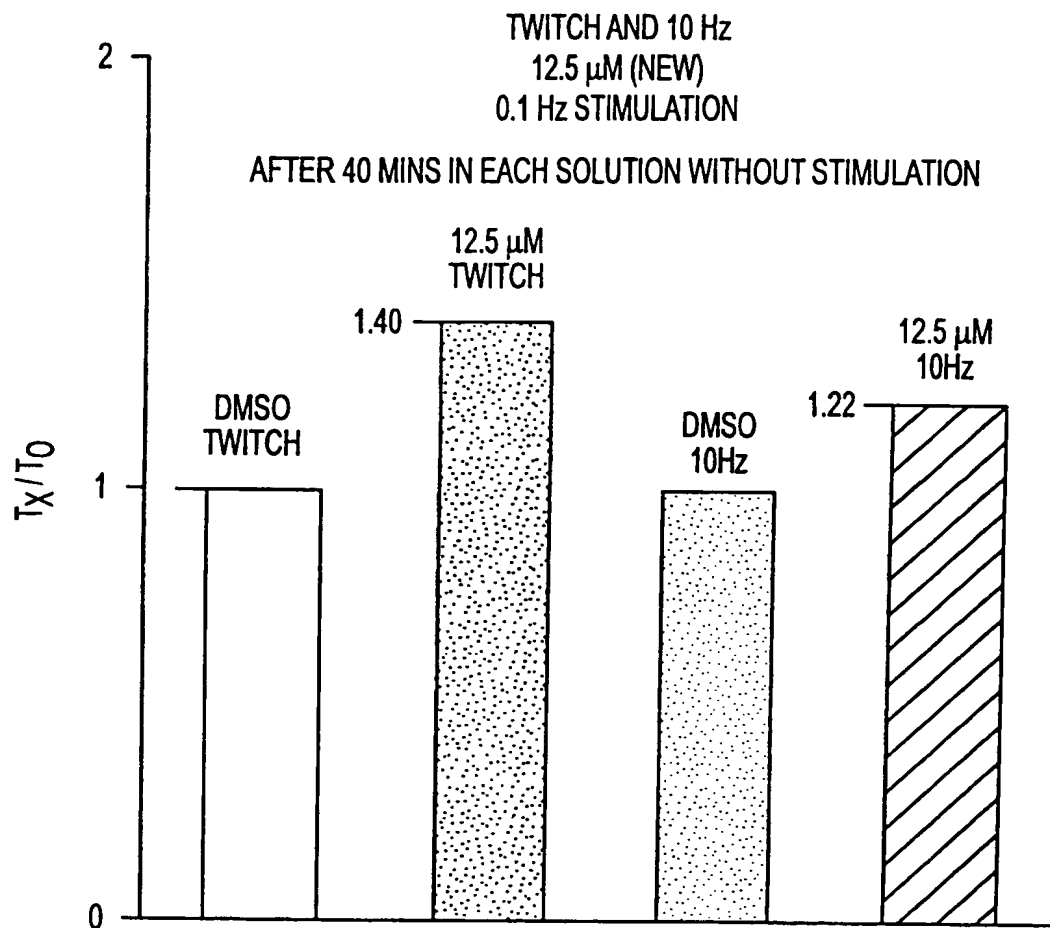


FIG. 20

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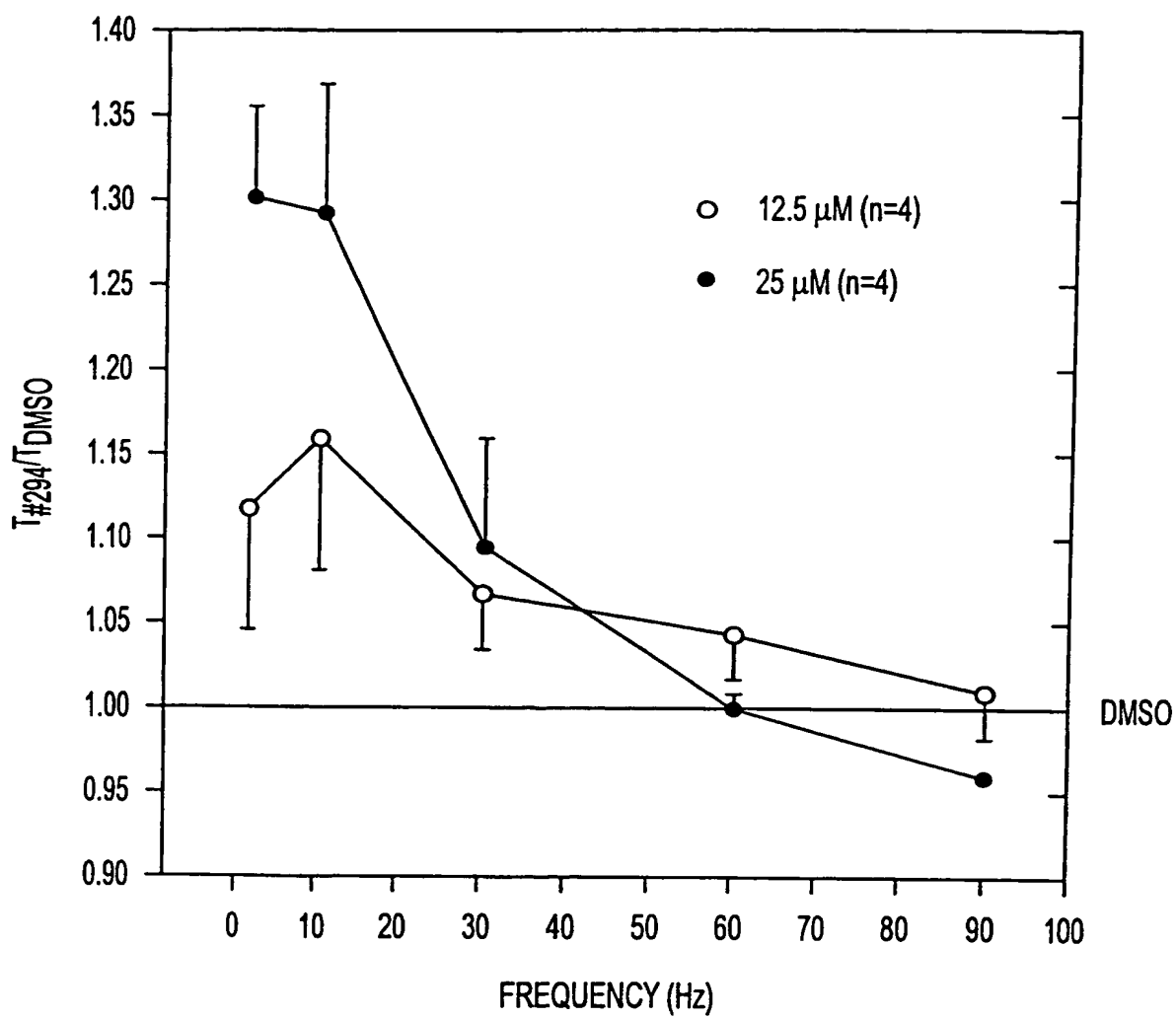


FIG. 21A

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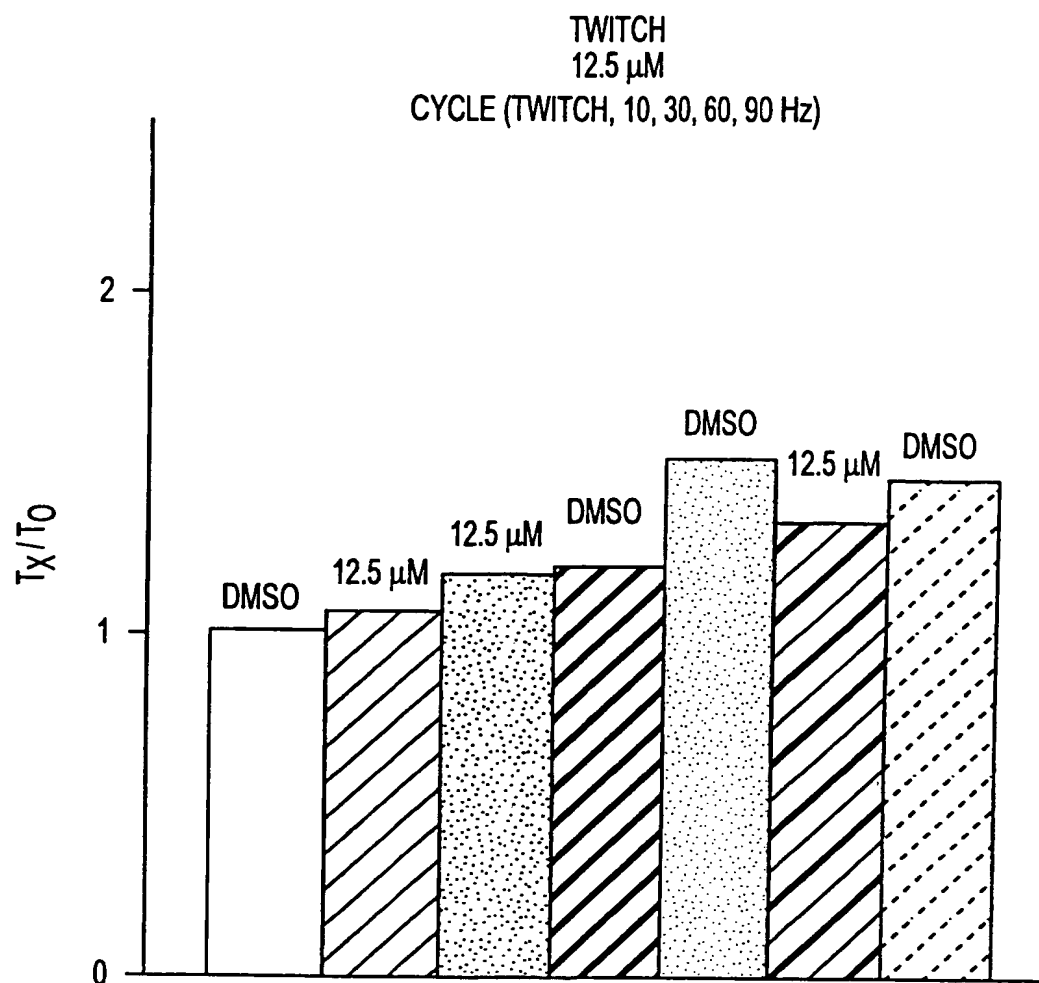


FIG. 21B

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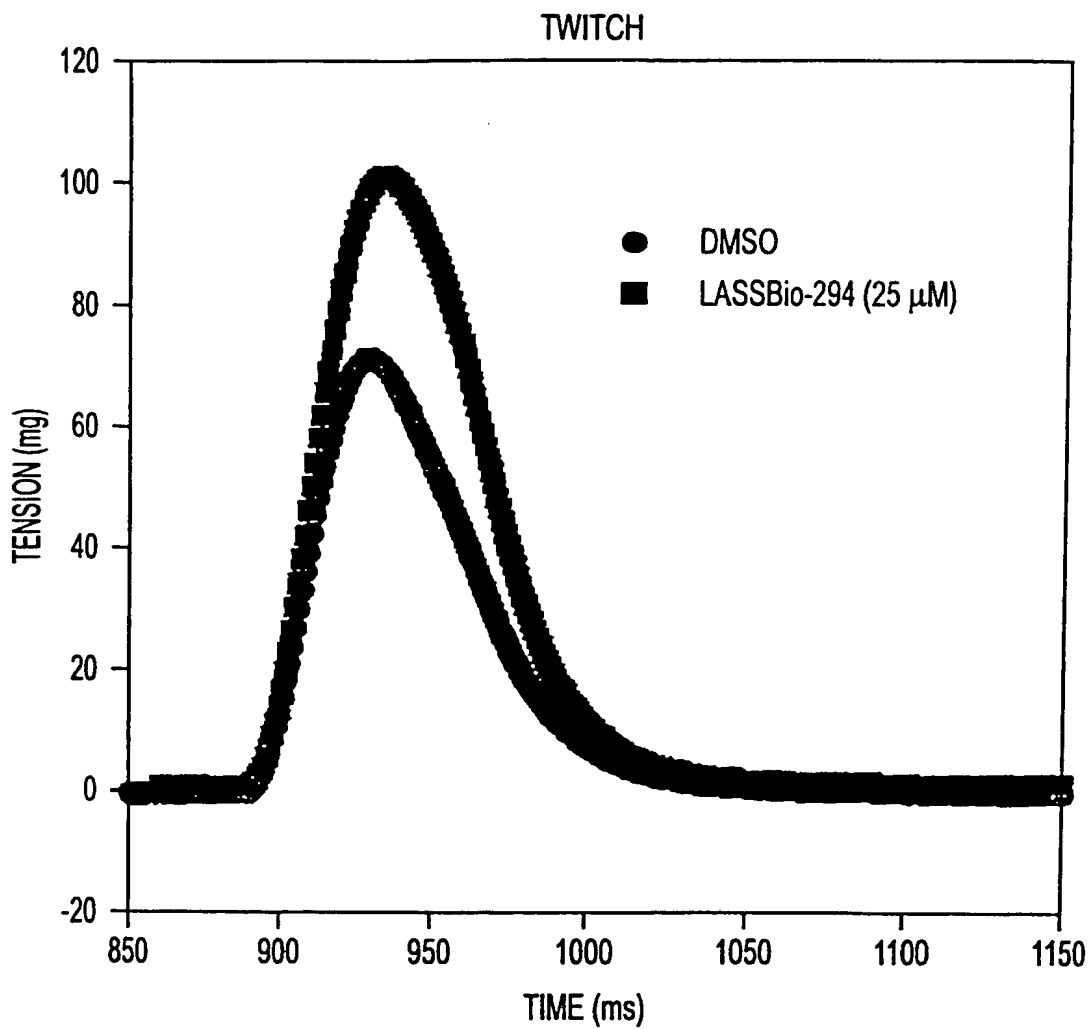


FIG. 22

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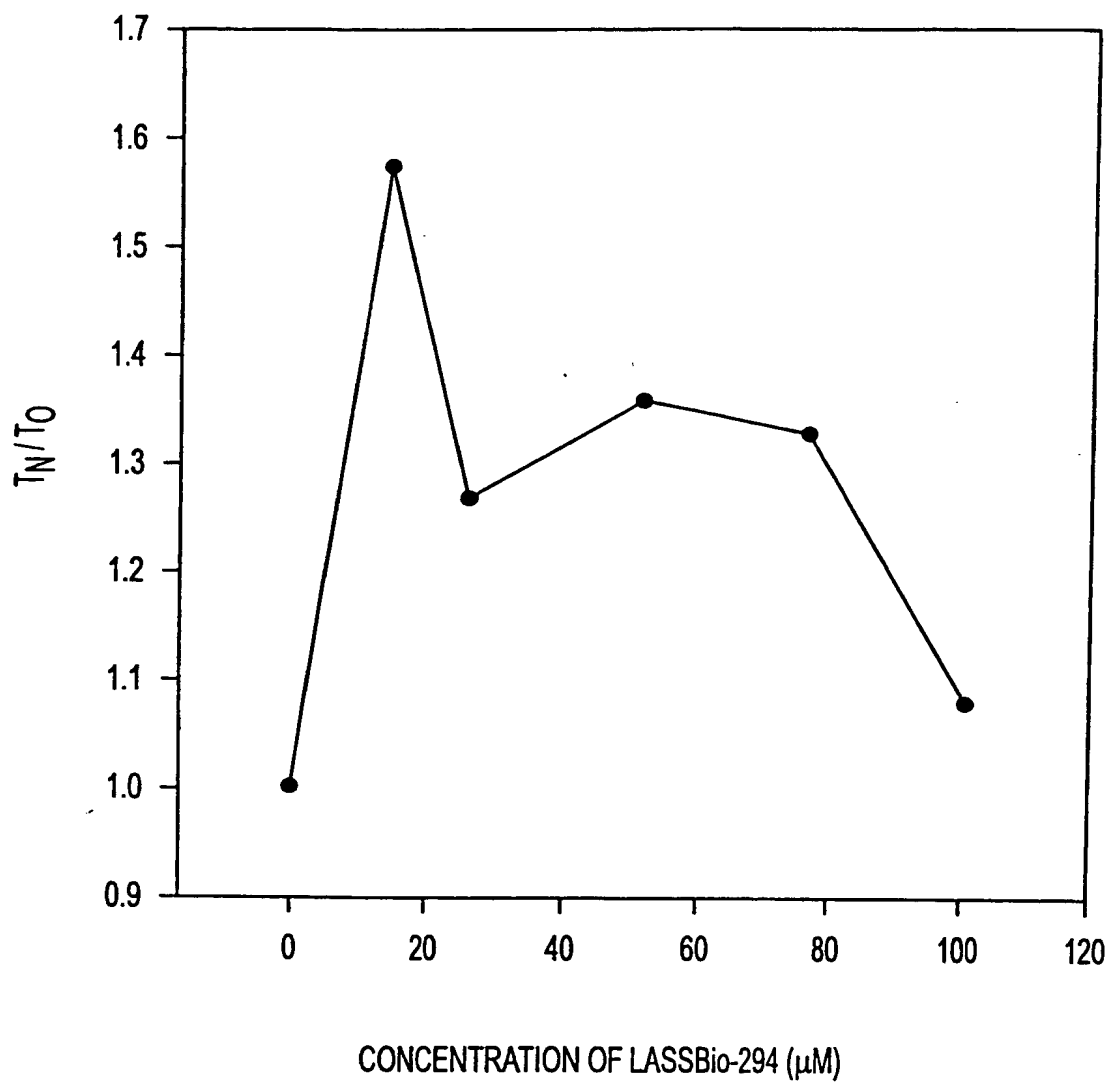


FIG. 23

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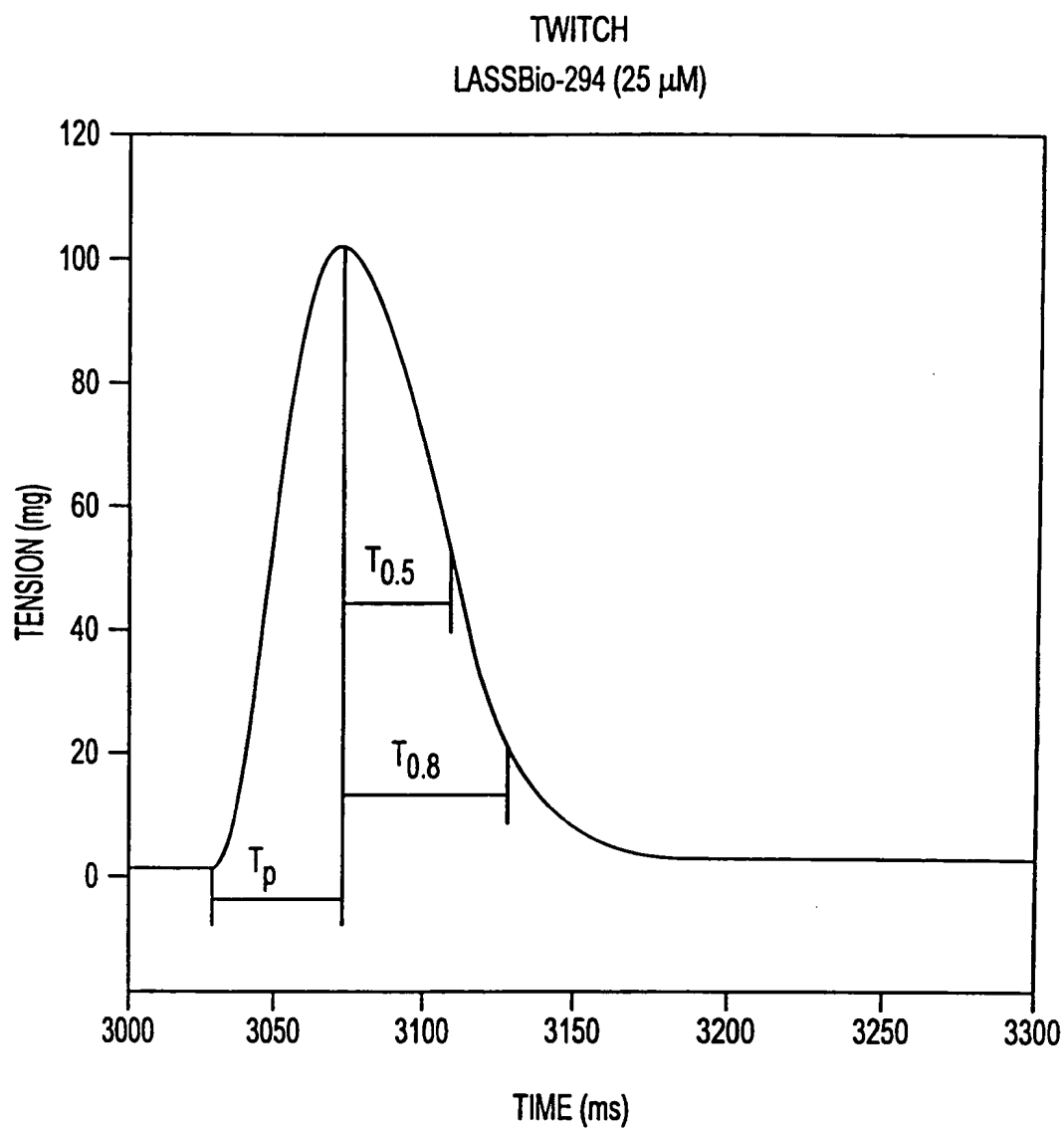


FIG. 24

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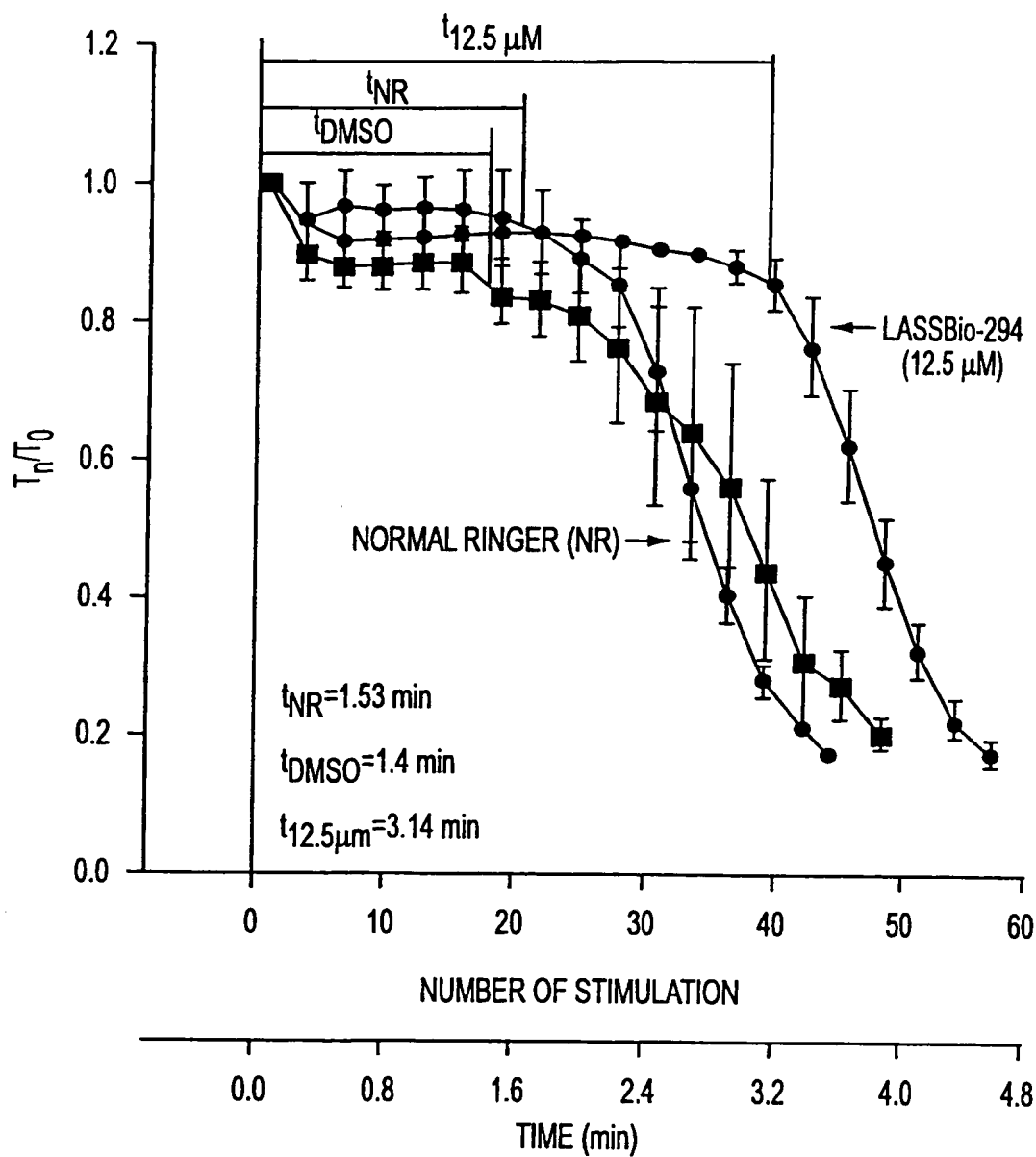


FIG. 25

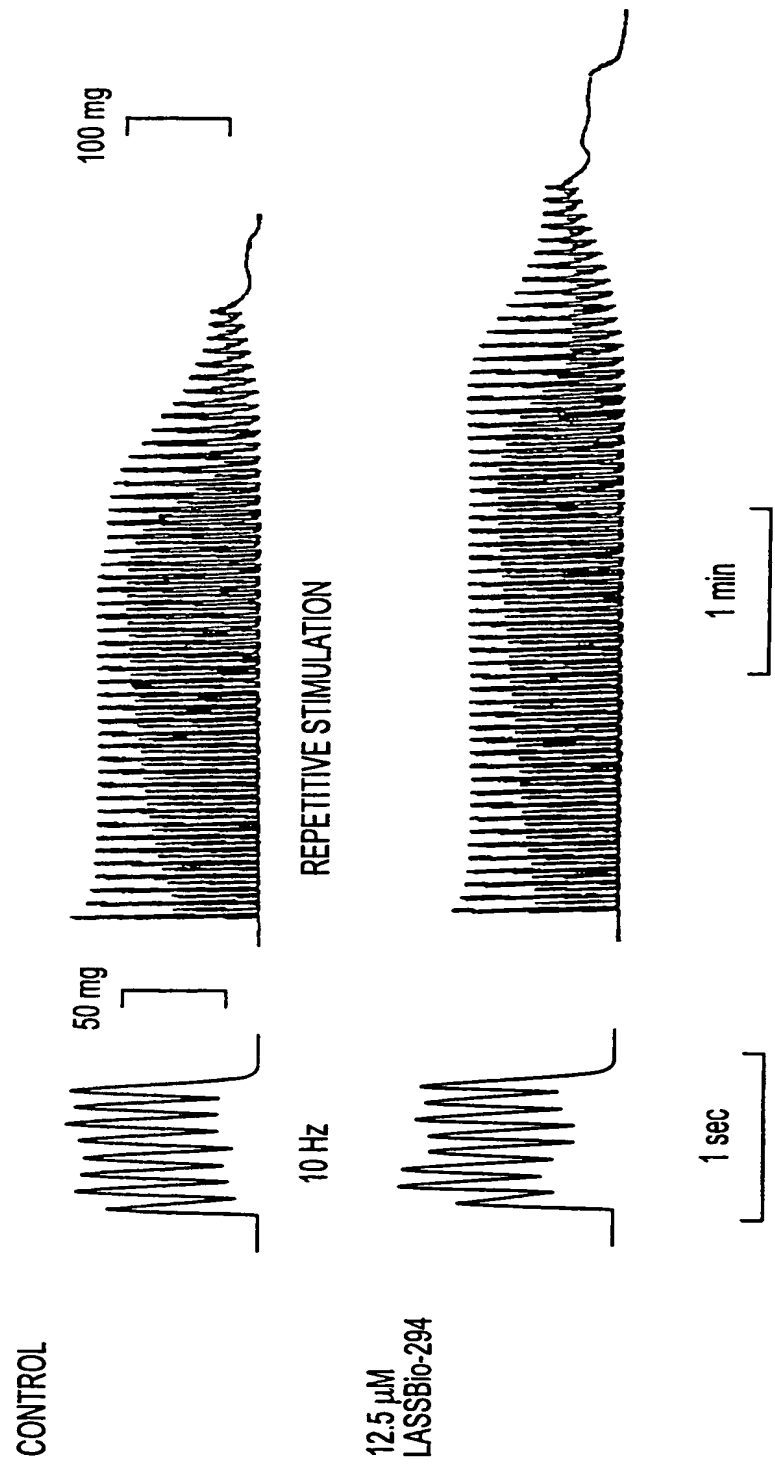


FIG. 26A

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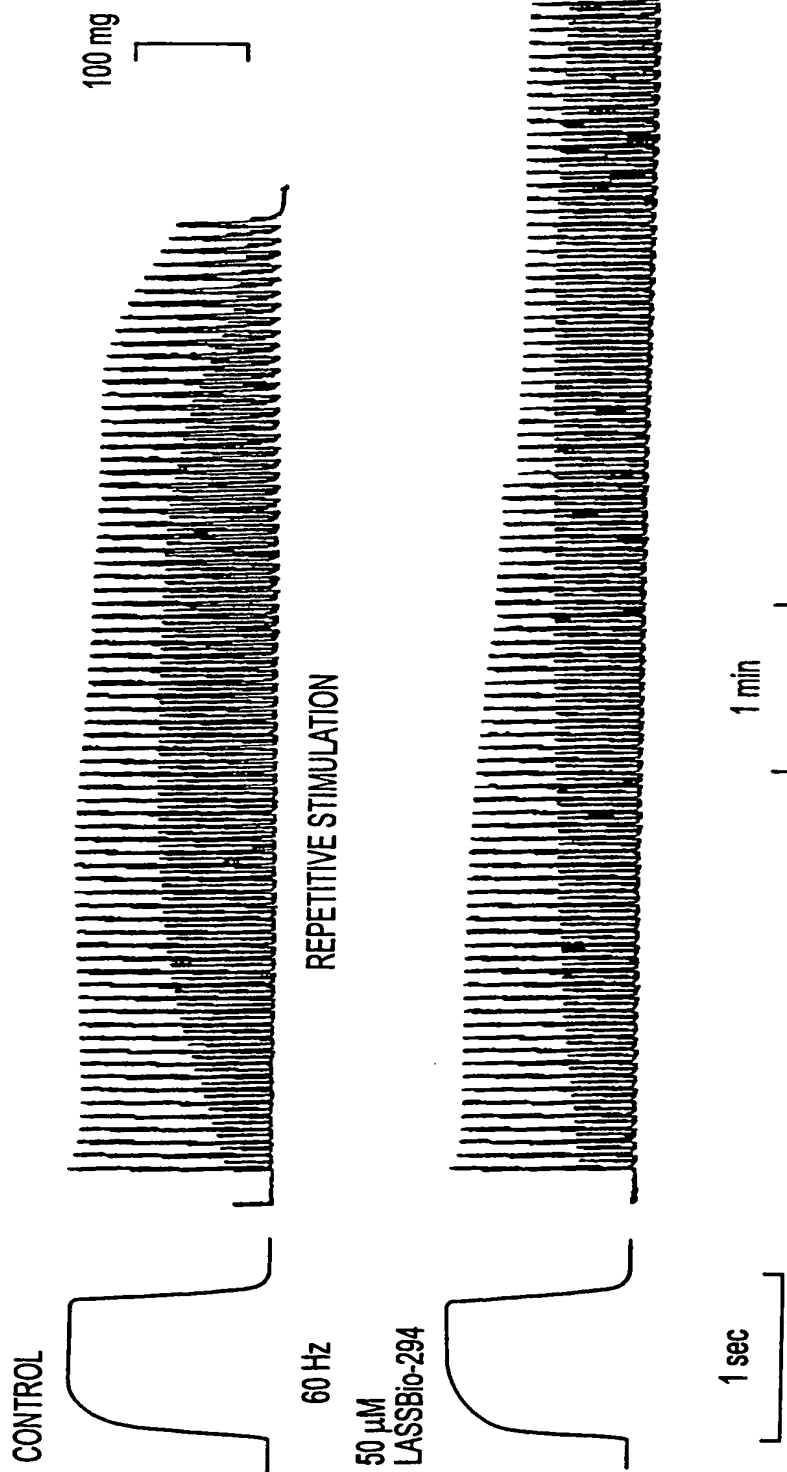


FIG. 26B

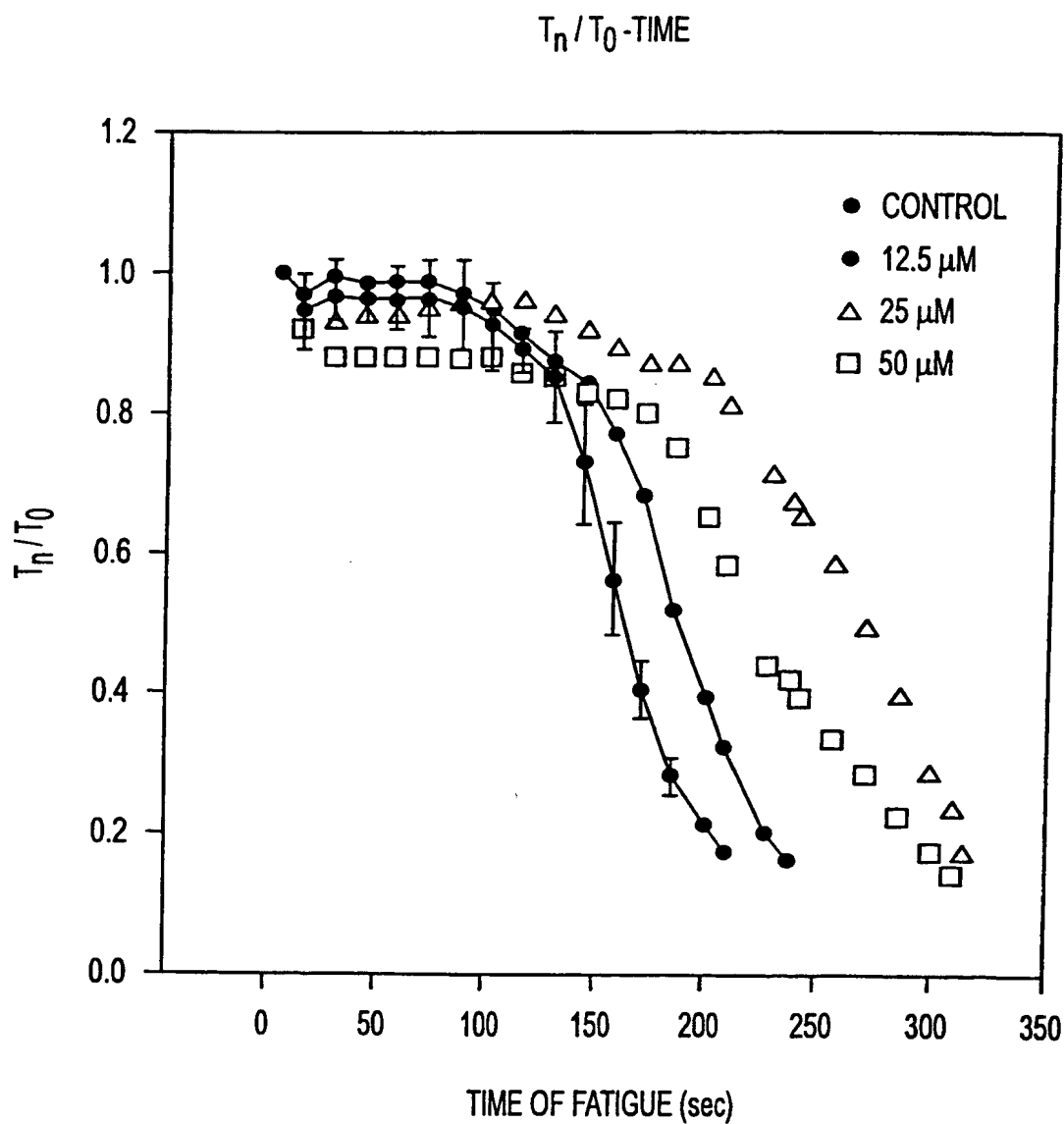


FIG. 27

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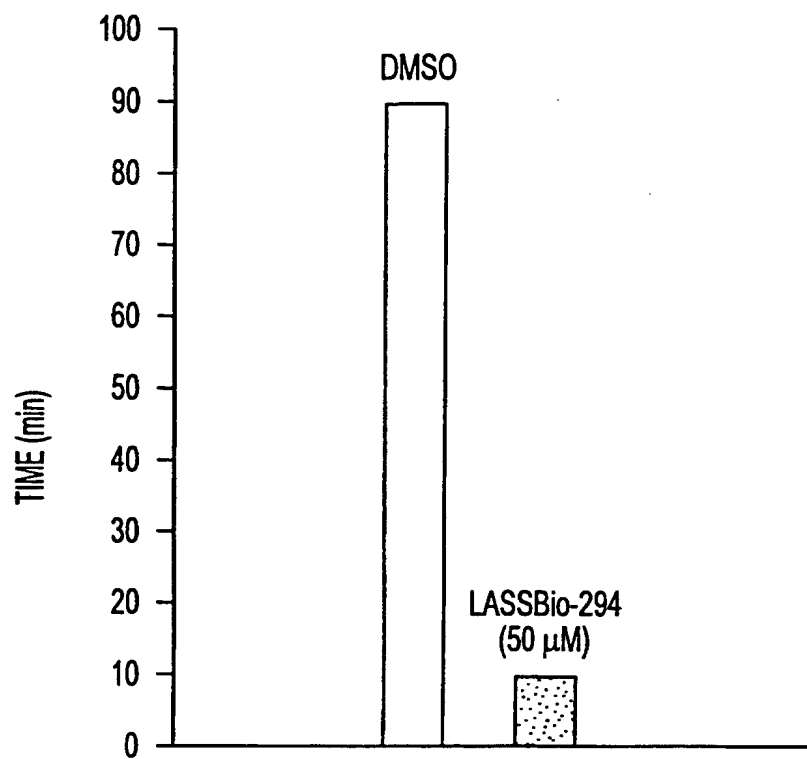


FIG. 28

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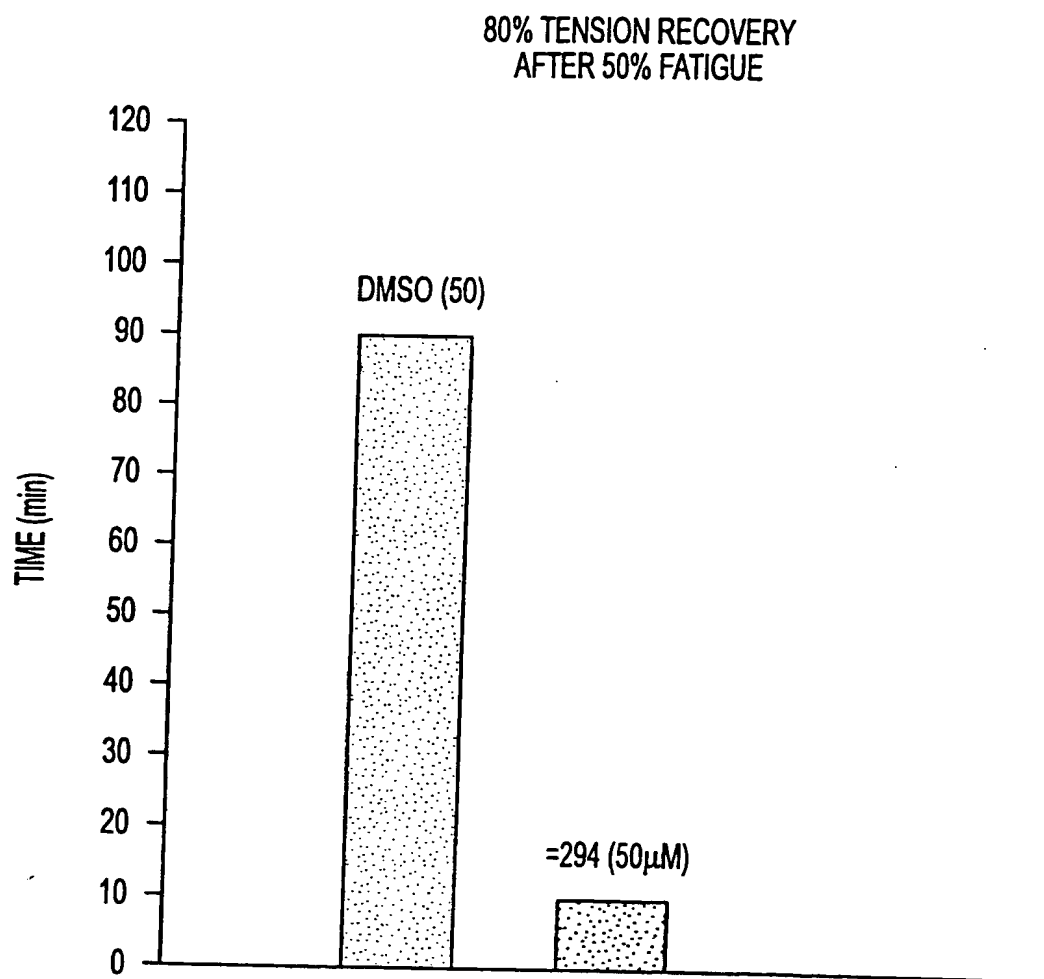


FIG. 29

NEUROMUSCULAR TRANSMISSION IS NOT AFFECTED BY LASSBio-294

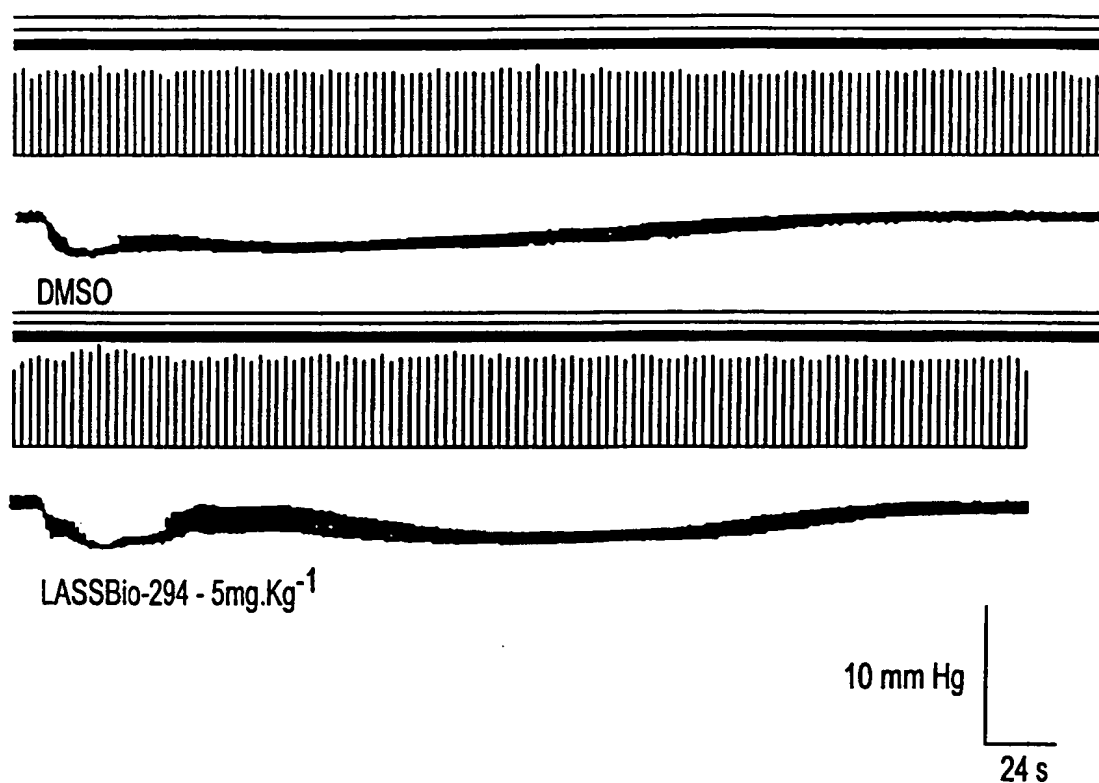
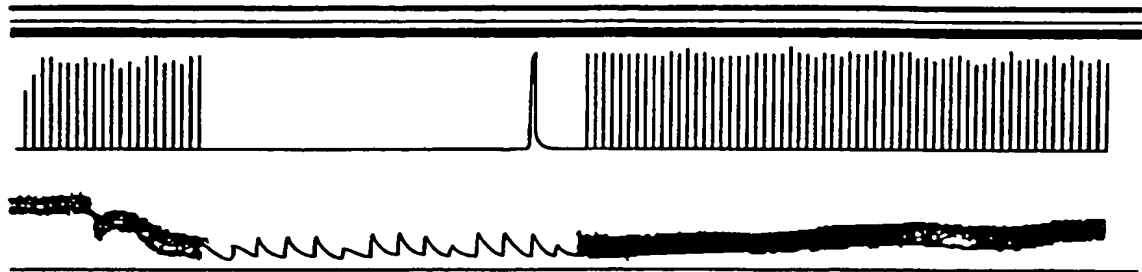


FIG. 30

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NEUROMUSCULAR TRANSMISSION IS NOT MODIFIED BY
LASSBio-294

DMSO

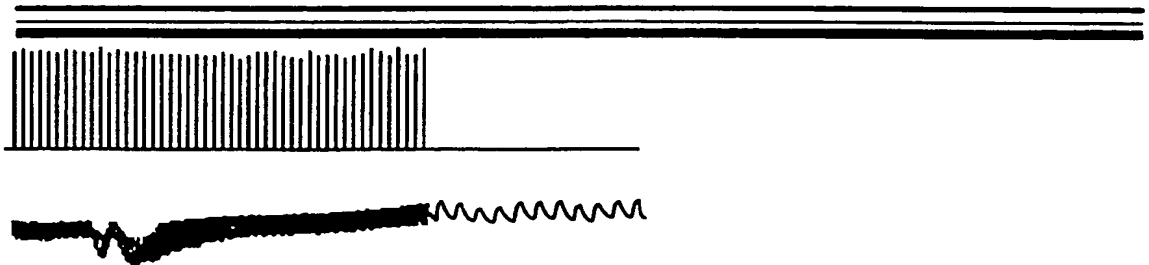
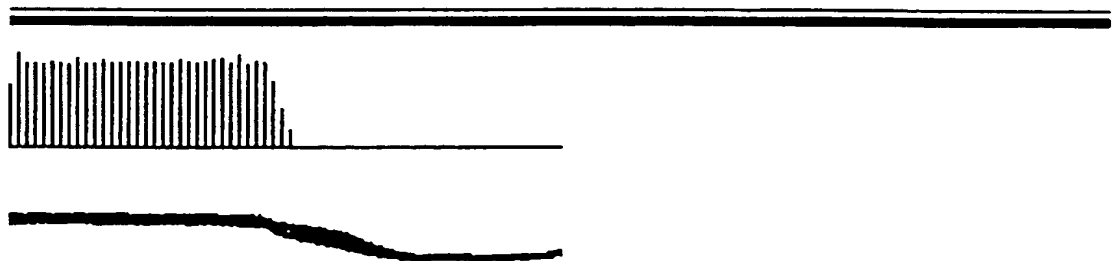
LASSBio-294 1mg.Kg⁻¹ALLOFERINE 0.6 mg.Kg⁻¹

FIG. 31

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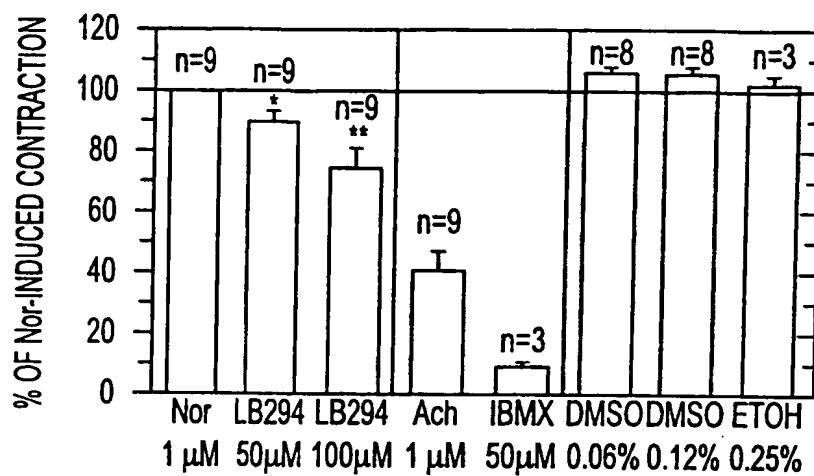


FIG. 32

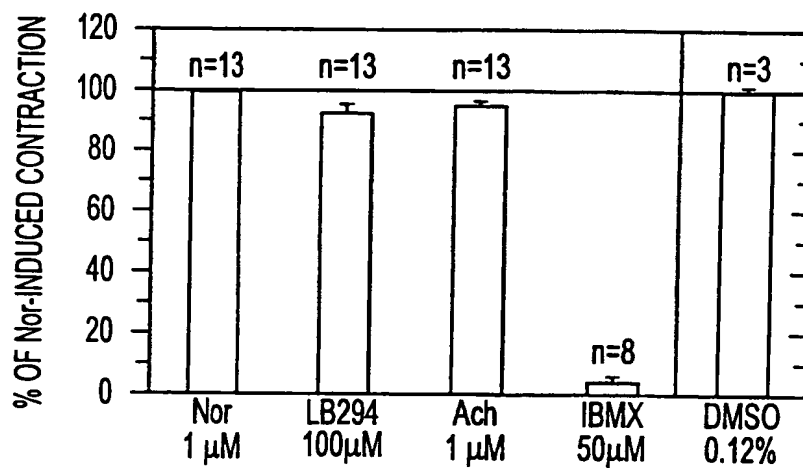


FIG. 33

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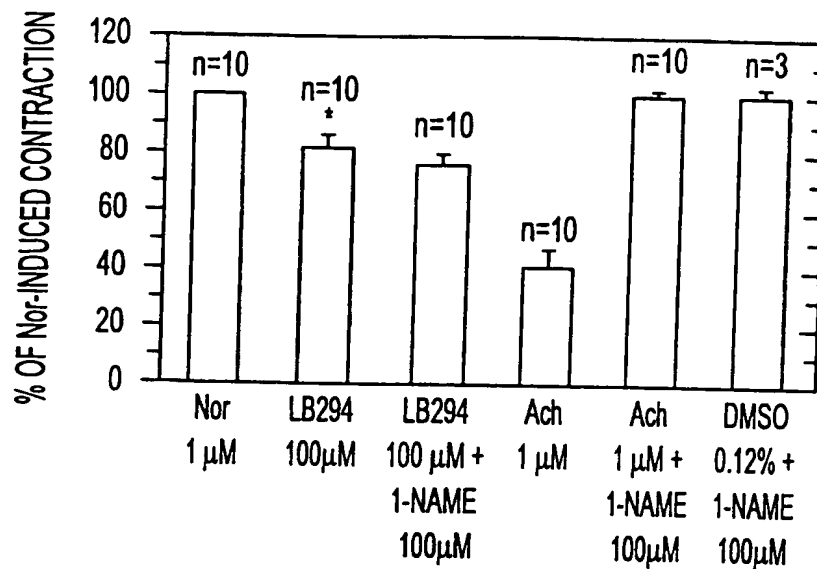


FIG. 34

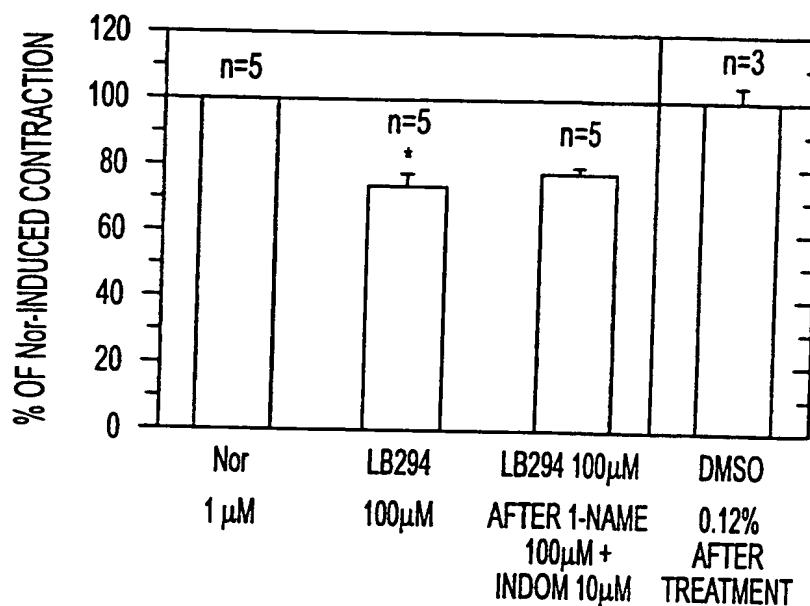


FIG. 35

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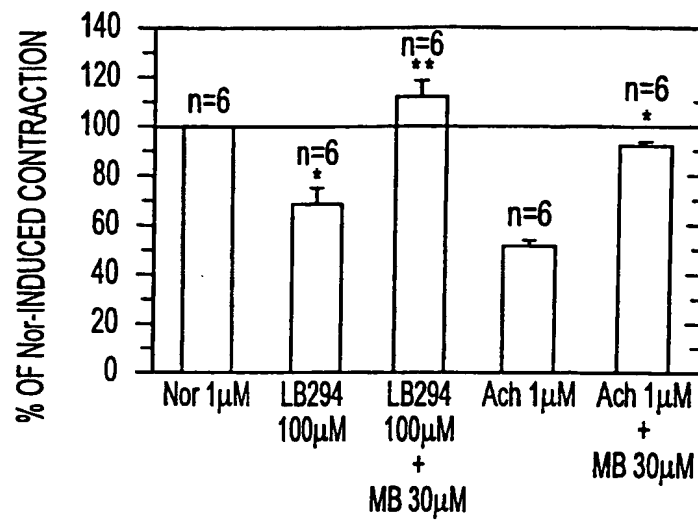


FIG. 36

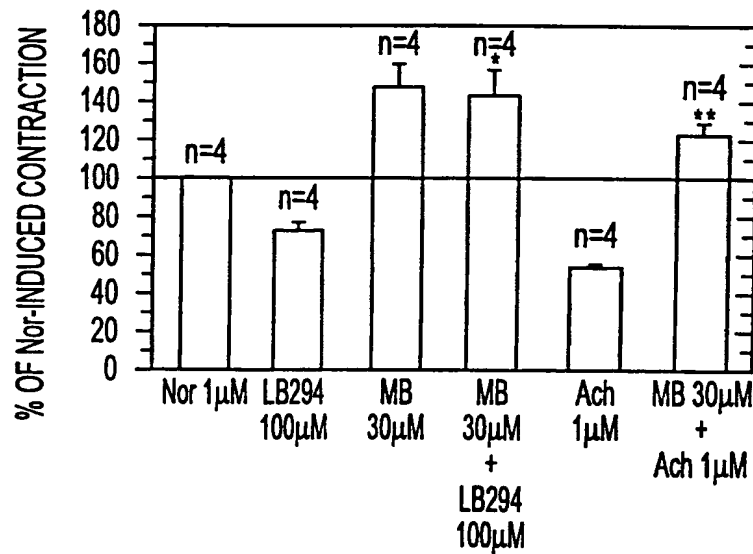


FIG. 37

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